University of Alberta

Patterns of Cortical and Trabecular Bone Loss in a Medieval British Skeletal Sample

by

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DEDICATION

This thesis is dedicated to the memory of my father, Alfredo (1936-2000).
You are greatly missed.

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CHAPTER ONE: INTRODUCTION

Osteoporosis is a heterogeneous disorder, characterized by low bone mass and microarchitectural deterioration of osseous tissue, resulting in severe skeletal atrophy, compromised skeletal strength, and an increased occurrence of non-traumatic fractures (Avioli and Kleerekoper, 1998; Kanis, 1996; Ross, 1998). Risk factors contributing to the etiology of this disorder include: increasing age (Kholsa et al., 1995; Riggs and Melton, 1986), genetic predisposition (Nguyen et al., 2000; Rubin et al., 2000), "race" (Luckey et al., 1989; Pollitzer and Anderson, 1989), female reproductive history (Tudor-Locke and McColl, 2000), and a variety of lifestyle choices, specifically dietary intake (Heaney et al., 2000), cigarette smoking (Jones and Scott, 1999), levels of physical activity and body weight (Marcus, 1996). Although clinical research has demonstrated that the risk and prevalence of osteoporotic fracture can vary dramatically between groups of different biogeographic and ethnic origins (National Osteoporosis Foundation, 1998; Villa, 1994), the longevity experienced by most modern human populations has led to a definitive increase in this disorder in both men and women. It is estimated that 1.4 million Canadians suffer from osteoporosis and that one in four women and one in eight men over fifty years of age will eventually develop this disease, resulting in medical expenditures in excess of 1.3 billion dollars per year (Osteoporosis Society of Canada, 2003). Given these estimates, it is evident why the study of bone loss and osteoporosis within a clinical setting is of vital importance to the long-term health and welfare of ageing populations. As stated by Weaver (1998), however, an important question for the bioarchaeologist is whether or not the paleopathological examination of bone loss and subsequent osteoporotic fracture can provide relevant data concerning the etiological processes and patterns of this common modern-day disorder.

A primary goal of paleopathological inquiry is to provide information concerning the physiological response of the human skeleton to stress and to place that response within a historical context from which human adaptations to specific stressors can be compared and evaluated (Agarwal and Grynpas, 1996; Ortner, 1991; Ubelaker and Grant, 1989; Walker, 2000). Many researchers incorporate this goal into their research design, generating data related to bone loss and fracture prevalence in past peoples – individuals who likely maintained lifestyles very different from those experienced by most modern-day inhabitants (Dequeker et al., 1997; Mays, 2000; Mays et al., 1998). These differences, in turn, may provide insight into which contributory factor(s) and/or lifestyle situation(s) predominate in the development and prevention of this multi-faceted disease. However, a review of the literature reveals that the paleopathological examination of both osteopenia and osteoporosis emphasizes the quantitative and qualitative loss of cortical bone (e.g. Cho 2002; Drusini et al., 2000; Mays, 2000; Mays, 1996; Rekewant, 1994), with fewer studies evaluating aspects of diminished quantity and quality in trabecular tissues (e.g. Agarwal, 2001; Agarwal et al., 2004; Vogel et al., 1988). This emphasis occurs despite clinical evidence suggesting that reductions in both the quantity and structural quality of trabecular bone greatly contributes to osteoporotic fracture risk and development (Cummings, 2002; Schnitzler, 1993; Turner and Burr, 1993).

Given that quantitative and qualitative reductions in both cortical and trabecular bone influence the development of osteoporosis and that age is considered to be an etiological factor in the micro-structural decline of trabecular bone in modern individuals (Britton and Davie, 1990; Parfitt et al., 1983), it is the first objective of this research to examine the relationship between age, trabecular bone quality of the iliac crest, and cortical and trabecular bone quantity of the radius in a Medieval British skeletal sample. The second objective is to determine the methodological feasibility of utilizing trans-iliac bone cores in the qualitative examination of archaeological skeletal material. This particular methodology was chosen for three reasons. First, current clinical study uses trans-iliac bone cores, or biopsies, as a preferred method for the structural assessment of osteoporosis and other metabolic bone diseases (Parfitt, 1992; Rao, 1983). By employing the same experimental protocol, this research will provide paleopathological data that is methodologically comparable to bone quality data generated from modern-day individuals. Second, the trans-iliac bone core, when compared to other methods of histomorphometric sampling, minimizes the tissue destruction of non-reproducible archaeological skeletal material and provides specimens with nominal architectural distortion, thereby facilitating structural analysis (Foldes et al., 1995; Rao, 1983). Finally, if the trans-iliac bone core is proven to be a reliable method for the structural assessment of trabecular bone in archaeological skeletal material, this would provide yet another methodological option for bioarchaeologists interested in the examination of bone loss in past populations.

Whereas the preceding paragraphs present the objectives of this research, the following chapters will offer an in-depth analysis of both osteopenic and osteoporotic bone loss in the past and present. Chapter Two describes the clinical classification of osteoporosis and emphasizes those risk factors thought to causally contribute to the onset and progression of this disease in contemporary populations. Chapter Three reviews the paleopathological evidence of osteopenic bone loss and osteoporotic fracture development. Various hypotheses concerning the etiologies of these disorders in the past, specifically dietary deficiencies, physical activity levels and female reproductivity patterns, are then examined. Chapter Four introduces the skeletal materials employed in this study and presents the methods used to conduct the research. Limitations associated with both the materials and methods are also addressed. Chapter Five presents the findings of this research. Observed patterns of age-related changes in cortical and trabecular tissues are compared with those reported in similar studies and interpretations pertaining to the etiology of bone loss noted in this Medieval British skeletal sample are presented and discussed. Chapter Six offers the differential diagnosis of an interesting outlier, individual G275, and chapter Seven provides a technical note on the utility of the chosen methodology for the collection and evaluation of histomorphometric data from archaeological skeletal material.

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CHAPTER TWO: CLINICAL CLASSIFICATION OF OSTEOPOROSIS AND ASSOCIATED RISK FACTORS

2.1. INTRODUCTION: WHAT IS OSTEOPOROSIS?

Osteoporosis, the most prevalent age-related metabolic bone disease in North America (Kanis, 1996), is characterized by substantial decreases in both bone mass and quality, leading to the development of non-traumatic fractures (Avioli and Kleerekoper, 1998; Brickley, 2000; Heaney et al., 2000). It is the incidence of these fractures that clinically distinguishes osteoporosis from osteopenia, another metabolic bone disorder characterized by low bone mass but without fracture development (Ross, 1998). Osteoporotic fractures tend to predominate in areas of trabecular bone, specifically the spine, wrist and hip, with the latter two typically associated with falls to the floor (Kholsa et al., 1995; Lindsay, 1995; Melton, 1995; Stini, 1995). To better understand how bone mass and quality influence the development of these fracture types, these terms will be defined in the following paragraphs.

Bone mass refers to the quantity, specifically the bone mineral content (BMC) or density (BMD), of the skeleton at any given point in time (Hays, 2000). Accumulated throughout maturation, peak skeletal mass is attained by humans between 25-35 years of age; after which it is diminished by the progressive, age-associated loss of bone (Heaney et al., 2000; Riggs and Melton, 1986). Following the general principle that equates increased mass with augmented skeletal strength (Heaney and Matkovic, 1995), medical practitioners most commonly employ BMC (grams) and BMD (grams/cm^2) to evaluate an individual's propensity to sustain an osteoporotic fracture (Hays, 2000). However, several researchers have demonstrated that measurements of bone mass are imprecise predictors of skeletal fragility and fracture risk in both human and animal models (e.g. Cerroni et al., 2000; Madhok and Allison, 2000; Schintzler, 1993; Thomsen et al., 1998); thus concluding that, although the attainment of an optimal peak bone mass decreases the progressive effects of age-associated bone loss, it does not necessarily prevent fractures.

In contrast to quantity, bone quality is a term that incorporates three interdependent indicators of skeletal strength and rigidity (Grynpas et al., 2000). In the adult human, there are two distinct types of bone: compact, which is a solid dense matrix found in bone shafts and on external bony surfaces; and trabecular, or "spongy" bone, which is located in the ends of all long bones and within flat or irregular skeletal elements, such as the sternum, pelvis and vertebrae (Keaveny et al., 2001). Trabecular bone is a porous tissue, formed by an interconnected, three-dimensional latticework of thick vertical columns and thinner horizontal struts separated by spaces filled with bone marrow and cells (Jenson et al., 1990; Kanis, 1996; Keaveny et al., 2001). These columns, struts and spaces are orientated in accordance to the compression and torsional stresses most commonly applied to a particular skeletal element, thereby maximizing that element's mechanical stiffness and functional strength (Currey, 1990; Kanis, 1996; Keaveny et al., 2001). The first quality indicator, the micro-architectural structuring of trabecular bone, measures the number, thickness, and connectivity of these columns and struts, as well as the dimensions of the marrow spaces (Lundon and Grynpas, 1993;

Turner and Burr, 1993; Vesterby, 1990). Hypothetically, factors such as increasing age, declining hormone levels, inadequate nutrition, and insufficient levels of weight bearing activity, can alter the connectivity, integrity and dimensions of these microstructures and severely compromise trabecular strength and rigidity (Schnitzler, 1993).

The second quality indicator, the biomechanical resiliency of the skeleton, measures the amount of stress trabecular bone can withstand under different loading conditions (Burr et al., 1997; Turner and Burr, 1993). Bone that is not biomechanically resilient is susceptible to fatigue damage or cracking (Cummings, 2002; Turner and Burr, 1993). When this damage becomes sufficiently severe the application of even small loads can lead to bone breakage (Turner and Burr, 1993). Consequently, decreased skeletal resiliency may help explain the non-traumatic nature of many osteoporotic fractures (Turner and Burr, 1993).

The third indicator, the level of skeletal remodeling, evaluates the processes of bone resorption and formation, specifically the degree of matrix mineralization, the amount of porosity, and the skeletal response to fatigue damage in compact bone (Burr, 1980). Whereas skeletal remodeling does occur in trabecular tissue, the solid structure of compact bone allows the remodeling process to be more easily observed microscopically. Due to its porous nature and rapid turnover rates, however, trabecular bone is usually the first skeletal tissue to be resorbed in situations of serum calcium deficiency, hormonal imbalance, or illness, and with increasing age (Stini, 1995; 1990)[1]. This resorbed tissue may or may not be replaced; thus the rate of skeletal remodeling has very important ramifications for the mechanical strength and rigidity of trabecular tissue.

2.1.2. Skeletal remodeling

Skeletal remodeling is the life-long renewal of bone through the cyclical resorption of mechanically or pathologically stressed tissue and the replacement of said tissue with newly synthesized bone matrix (Jilka, 1998). These processes of bone resorption and formation are performed by teams of cells, or bone remodeling units (BRUs), which are made up of osteoclastic and osteoblastic bone cells (Dempster, 1995; Rodan et al., 1996).

Hematopoietic in origin, osteoclasts are highly specialized, multi-nucleated cells localized on the endosteal surfaces of bone (de Vernejoul, 1998; Jilka et al., 1992). Functioning in a resorptive capacity, osteoclasts employ a specialized membrane, or "ruffled border", to invaginate bony surfaces, degrading bone matrix through the production of proteolytic enzymes and hydrogen ions (Vaananen, 1996; de Vernejoul, 1998). Osteoclasts can also degrade collagen, an organic extracellular matrix protein, through the excretion of cathespin-K enzymes (Robey, 1995; de Vernejoul, 1998). *In*

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[1] It should be noted that the osteoclastic resorption of bone is not necessarily the first response to serum calcium deficiency. Several researchers hypothesize that blood-calcium homeostasis may also be regulated by the osteocyte through a localized bone remodeling process called osteocytic osteolysis (Nijweide et al., 2002; Shipman et al., 1985). This process is regulated by two hormones, the parathyroid hormone and calcitonin, which function to increase and decrease circulating levels of ionic calcium and phosphate respectively (Shipman et al., 1985).

vitro studies demonstrate that osteoclasts cycle between resorbing and non-resorbing phases, with each cell contributing to more than one resorption cycle (Vaananen, 1996).

Osteoclastic bone cell formation is controlled by several endocrinological agents, including 1,25-dihydroxyvitamin D_3 (Duong and Rodan, 2001; Takahasi et al., 2002), the parathyroid hormone (PTH) (Duong and Rodan, 2001; Takahasi et al., 2002), prostaglandin E_2 (Duong and Rodan, 2001; Lader and Flanagan, 1998; Takahasi et al., 2002) and the cytokines tumor necrosis factor (TNF), growth factor M-CSF (Macrophage Colony-Stimulating Factor), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-11 (IL-11) (Ahlen et al., 2002; Gowen et al.,1983; Jilka et al., 1992; Lader and Flanagan, 1998; Pacifici, 1998). Several of these agents, specifically PTH, TFN, and IL-1, in conjuction with estrogen, function interdependently to control the frequency of osteoclastic recruitment and the intensity and duration of osteoclastic activity (Jilka et al., 1992; Pacifici, 1998; Rodan et al., 1996).

In contrast to the resorptive capacities of osteoclasts, osteoblasts perform multiple formative functions including: (i) the active secretion of unmineralized bone matrix (osteoid) and growth factors, (ii) the deposition of these growth factors into the pre-existing bone matrix, and (iii) the mineralization of the osteoid (Aubin and Lui, 1996; de Vernejoul, 1998). In conjunction with these formative functions, osteoblasts also assume a regulatory role in the resorption cycle by synthesizing the osteoclast-recruiting cytokines IL-6 and M-CSF, both of which play a critical role in the proliferation and differentiation of osteoclast progenitors (de Vernejoul, 1998; Doung and Rodan, 2001; Eriksen et al., 1988; Komm et al., 1988); and by producing osteoprotegerin (OPG), a protein that inhibits osteoclastogenesis both *in vivo* and *in vitro* (Takahasi et al., 2002).

Despite the differences in function, osteoblasts, like osteoclasts, are controlled by several endocrinological agents including PTH, 1,25 dihyrdroxyvitamnin D_3, IL-6, and prostaglandin E_2 (Aubin and Triffitt, 2002). In addition, receptors for androgen, estrogen, the transforming growth factors TGFβ and TGFβ type II, and the obese protein leptin have been identified on osteoblastic bone cells (Aubin and Triffitt, 2002; Gordeladze, 2002; Orwoll et al., 1991). It is currently hypothesized that estrogen prevents osteoblast apoptosis, while simultaneously promoting the cellular death of osteoclasts and their precursors, thereby balancing bone resorption and formation activities (Boyce et al., 2002). If proven to be correct, this hypothesis would help explain why cyclical resorption and bone loss increase in the estrogen-deficient states of naturally and surgically induced menopause.

Through the function of both osteoclasts and osteoblasts, bone is not only remodeled, but also modeled. In the latter, bone resorption and deposition occur independently of each other on the endosteal and periosteal surfaces of various skeletal locations, resulting in the alterations of bone size and shape that occur with growth (Martin, 2000; Vanderschueren and Bouillon, 1998). In contrast, the osteoclastic and osteoblastic activities associated with remodeling are performed as a coupled sequence on the same skeletal site, negating a change in shape but allowing for the maintenance of matrix integrity (Martin, 2000; Vanderschueren and Bouillon, 1998). It is estimated that 2-10% of the mature skeleton is remodeled per year through the initiation of a

series of cellular events by the BRUs (Dempster, 1995; Pacifici, 1998). These events include:

(i) Activation – the initial event whereby the quiescent surface of the bone, characterized by a thin layer of osteoblastic lining cells (Fig. 2.1a), attracts a team of pre-osteoclasts (Fig. 2.1b). Activation is likely caused by altered levels of various endocrinological agents (Frost, 2001), and mechanical strain as detected by the osteocyte (Nijweide et al., 2002). The most abundant bone cell type, the osteocyte represents the final differentiation stage of the osteoblastic cell line (Nijweide et al., 2002). It is hypothesized that osteocytes are the mechanosensory cells which, through the reception and interpretation of mechanical strain placed on the skeleton, sense where bone must be reinforced or removed and sends signals to the BRUs to initiate remodeling where needed (Martin, 2000; Mullender et al., 1998).

(ii) Resorption – through a series of endocrinological events, pre-osteoclasts differentiate and fuse to form the large, multi-nucleated osteoclastic cell (Duong and Rodan, 2001). Over a period of 4-12 days, these cells migrate from one resorption site to the next, dissolving the mineral component of bone, hydrolyzing the organic matrix and creating saucer-shaped excavations 40-60 micrometers (μm) deep (Fig. 2.1c) (Duong and Rodan, 2001). After this period, resorptive activity is arrested through a series of as yet unknown mechanisms, with the large multi-nucleated osteoclasts being replaced by smaller mononuclear cells (de Vernejoul, 1998) (Fig. 2.1d). These cells function to smooth over the newly excavated cavities. Following resorption, a reversal phase is initiated in which a cement-like substance rich in proteoglycans, glycoproteins and acid phosphates is deposited. This phase designates the interval of time, usually 7-10 days, in which the preceding resorptive processes are coupled to those of formation (de Vernejoul, 1998).

(iii) Coupling – during this phase, coupling mechanisms attract osteoblasts to the eroded bony surface and initiate the synthesis of the osteoid matrix (Kanis, 1996). Although the precise process(es) of coupling are not well understood, several endocrinological agents, specifically prostaglandin E_2, IGF-1, PTH, and TGFβ may play roles (Kanis, 1996; Ott, 2002; Stini, 1990; Rubin et al., 2002). Additional hypotheses include: (i) the resulting release of bone forming factors, particularly insulin growth factors (IGFs) or TGFβ, from the matrix during resorption leads to the stimulation of osteoblasts (Kanis, 1996), and/or (ii) the osteocytic response to mechanical strain instigates formation (Goldstein et al., 1990; Lanyon, 1984).

(iv) Mineralization - shortly after initial synthesis and formation, the osteoid matrix begins to mineralize (Fig. 2.1e) (de Vernejoul, 1998). This mineralization is marked by the presence of alkaline phosphatase (ALP), an ectoenzyme which is shed from the osteoblast into the extracellular fluid (Robey, 1995). Widely recognized as a biochemical marker of bone mineralization, the precise role of ALP is currently not known. It is hypothesized, however, that ALP functions to augment local levels of phosphate, a phospheric acid derivative which functions to maintain the blood's acid-

alkaline balance (Robey, 1995). Osteocalcin, another bone protein produced by the osteoblast, is also present during the process of mineralization, increasing mineral absorption rates in the newly formed matrix (Stini, 1990). In contrast to resorption, which usually takes days to perform, the osteoblastic formation of bone can require several months for completion (Kanis, 1996). Although osteoblasts vastly outnumber osteoclasts (Nijweide et al., 2002), in an abnormal metabolic environment bone resorption can surpass bone formation resulting in excessive loss of both bone quantity and quality (Dempster, 1995; Pacifici, 1998). However, in metabolic environments where the remodeling processes are balanced, both bone quantity and quality are maintained through the regularized rate of bone turnover (Fig. 2.1f).

2.2. THE CLINICAL CLASSIFICATION OF OSTEOPOROSIS

Osteoporosis is clinically categorized as primary or secondary, with the basis of categorization dependent upon the presence or absence of associated medical diseases, surgical procedures or medications known to adversely affect bone metabolism (Kholsa et al., 1995; Riggs and Melton, 1986). Although the clinical separation of these forms does suggest a degree of independence, their division is somewhat artificial as the causal mechanisms of one type may contribute to the incidence of the other in certain individuals (Kholsa et al., 1995).

2.2.1. Primary osteoporosis

Primary osteoporosis is further separated into idiopathic and involutional forms, with idiopathic osteoporosis afflicting both juveniles and young adults (Kholsa et al., 1995). Idiopathic juvenile osteoporosis (IJO) is a relatively uncommon disorder, affecting previously healthy children of both sexes between the ages of eight to fourteen (Kholsa et al., 1995). Characterized by diffuse pain in the back and extremities combined with radiological evidence of multiple fractures typically occurring at the metaphyses and vertebral bodies (Lorenc, 2002), the pathophysiology of IJO is not well understood. Results from histomorphometric analyses of iliac crest bone biopsies indicate that IJO patients have severely impaired osteoblast function on trabecular surfaces, resulting in decreased bone formation rates and thickness and number of trabeculae (Rauch et al., 2002; Rauch et al., 2000). IJO also inhibits the rate of endocortical modeling, leading to decreased internal cortical width (Rauch et al., 2002). Periosteal modeling is unaffected, however, suggesting that IJO is likely caused by factor(s) which predominantly affect bone formation on surfaces exposed to marrow cells (Rauch et al., 2002).

Although more prevalent than the juvenile form, the incidence of idiopathic osteoporosis in young adults is still relatively infrequent. Occurring equally in both men and women, clinical presentation is extremely varied, suggesting that more than one physiological process may be involved (Kholsa, 1997; Kholsa et al., 1995). Like IJO, impaired osteoblast function is a contributor to the development of idiopathic osteoporosis, leading to a metabolic balance favoring resorption and, ultimately, a net loss of bone (Johansson et al., 1997; Kurland et al., 1997). Mild manifestations of the

disease may include multiple fractures of the ribs, metatarsals and the vertebral column, with the latter resulting in the loss of height (Kholsa et al., 1995). Patients who are severely afflicted may experience unilateral or bilateral hip fractures, progressive incapacitation and death (Kholsa et al., 1995).

In contrast to the preceding idiopathic forms, involutional osteoporosis is very common, beginning in mid-life and increasing in incidence and severity with age (Kelly, 1999; Kholsa et al., 1995). On the basis of clinical features, densitometric measurements and hormonal changes, two separate "types" or syndromes have been identified within the involutional category, each with their own pathophysiological characteristics (Table 2.1). The heterogeneous physiology of these types has important clinical implications in terms of disease diagnosis, prevention and treatment (Kholsa et al., 1995).

2.2.2. Secondary osteoporosis

Whereas the involutional forms of osteoporosis are associated with age-related alterations in bone metabolism and the hormonal environment, the development of secondary osteoporosis can occur at any age and is commonly associated with a variety of pathogenic and iatrogenic factors (Tables 2.2[a] and [b]) (Stini, 1990). It is currently estimated that 25-30% of vertebral fractures in women, and up to 78% in men can be attributed to one or more factors associated with these secondary forms (Çakir et al., 2002; Reid and Harvie, 1997).

In addition to these pathogenic and iatrogenic mechanisms, there are a variety of other causal contributors, or "risk factors", associated with the progression of secondary bone loss and the exacerbation of the involutional forms. These include genetic predisposition, "race", female reproductive history and a bevy of lifestyle choices, specifically dietary intake, cigarette smoking, levels of physical activity and body weight.

2.3. THE ASSOCIATED RISK FACTORS OF OSTEOPOROSIS

2.3.1. Genetic predisposition

Researchers estimate that 50-80% of the variation found in skeletal BMD can be accounted for by genetic factors (Deng et al., 2000; Dequeker et al., 1987). While the reliability of these conclusions has been questioned, with Slemenda and co-workers (1991) suggesting that these estimates may be biased by the overestimation of gene interactions, there is little doubt that genetics do play an influential role in the acquisition of skeletal BMD in humans (Nguyen et al., 2000; Rubin et al., 2000). Currently, researchers have isolated several "candidate genes", each of which may contribute to the acquisition and maximization of skeletal BMD. These genes include:

(i) Calcium-sensing receptor gene (CaSR) – the calcium-sensing receptor (CaSR) is a plasma membrane protein that not only regulates the renal reabsorption of calcium, but also controls the secretion of PTH by the parathyroid gland (Vezzoli et al.,

2002). In situations of hypocalcaemia, PTH stimulates the osteoclastic resorption of bone, thereby releasing calcium from the skeleton; while, simultaneously, increasing the renal absorption of calcium and excretion of phosphorus, and augmenting the conversion of 25-dihydroxyvitamin D to 1,25 dihydroxyvitamin D_3 (Hock et al., 2002; Rubin et al., 2000). Mutations of the CaSR gene can adversely affect serum calcium homeostasis through alteration of these PTH and renal functions (Rubin et al., 2000; Vezzoli et al., 2002).

(ii) Estrogen receptor alpha gene (ER1) – ER1 has been identified as one of many genes responsible for the mediation of estrogenic responses within the skeleton, with its allelic variations predicting BMD at the lumbar spine and the femoral neck (Gennari and Brandi, 2001; Kobayashi et al., 1996; Rubin et al., 2000). However, current understanding of the ER1 gene in the pathophysiology of osteoporosis is controversial, with results differing dramatically between racial groups (Efstathiadou et al., 2001; Gennari et al., 1998; Han et al., 1997; Ho et al., 2000).

(iii) Insulin growth factor- 1 (IGF-1) gene – IGF-1 is structurally related to insulin and is one of the most ubiquitous polypeptide growth factors found in human plasma (Karasik et al., 2002). It is hypothesized that IGF-1 contributes to the linear growth of bone, promotes osteoclast recruitment as well as osteoblast differentiation, and is a mechanism used to couple resorption to formation within the bone remodeling cycle (Kanis, 1996; Karasik et al., 2002; Nijweide et al., 2002; Rosen, 1999). Low levels of circulating IGF-1 have been implicated in the pathophysiology of idiopathic osteoporosis in men, through the reduction of osteoblastic activity (Gennari and Brandi, 2001; Kurland et al., 1997). These low levels have been linked to a specific allelic configuration (a 192/192 polymorphism) of the IGF-1 gene (Bilezikian et al., 1999; Gennari and Brandi, 2001).

(iv) Transforming growth factor beta 1 (TGFβ1) gene - TGFβ1 is a multi-functional hormone that is essential for cellular growth and differentiation, wound healing, and morphogenesis (Rubin et al., 2000). TGFβ1 is also one of the many endocrinological agents that regulate the coupling of osteoclastic resorption to osteoblastic formation and osteoclast apoptosis (Kanis, 1996; Rubin et al., 2000; Yamada et al., 1999). Yamada and colleagues (1998) discovered that a T→ C polymorphism at nucleotide 29 of the signal sequence of the TGFβ1 gene, in which leucine (a nutritionally essential amino acid) is replaced by a proline residue, is significantly associated with BMD at the lumbar (L2-L4) spine in postmenopausal Japanese women. Those women who exhibited the C/C genotype had significantly lower frequencies of vertebral fractures when compared to women who were T/T homozygous or T/C heterozygous.

(v) Type I∝1 collagen gene (COLIA1) –Type 1 collagen is the main structural protein of bone, comprising 85% of the organic components found within the skeleton (Rubin et al., 2000). Given its predominance, genes encoding type 1 collagen (i.e. COLIA1 and COLIA2) are prime candidates for the genetic regulation of bone mass in

humans (Gennari and Brandi, 2001; Wolf et al., 2000). This primacy was initially demonstrated by Grant and colleagues (1996), who concluded that a common G (guanine) → T (thymidine) substitution (both the G/T (Ss) heterozygote and the T/T homozygote (ss)) in the regulatory region of COLIA1 at the recognition site for the transcription factor Sp1 occurred at significantly higher frequencies in individuals with reduced BMD and vertebral fractures. These preliminary results were confirmed by subsequent studies (Keen et al., 1999; Langdahl et al., 1998; Uitterlinden et al., 1998). However, in their study of 1778 post-menopausal women, Uitterlinden and co-workers (1998) found that the relative risk of osteoporotic fracture was 2-3 times greater than that predicted by the COLIA1 genotypes, even after adjustment for body weight and bone density. Given this finding, the authors concluded that the COLIA1 polymorphism may also mark differences in bone quality, specifically in the micro-architecture of the skeleton.

(vi) Vitamin D-receptor (VDR) gene – Vitamin D is most commonly produced by the dermal conversion of 7-dehydrocholestrol after exposure to ultra-violet solar radiation (Vanderschueren and Bouillon, 1998). Following this conversion, vitamin D is transported through the plasma to a vitamin-D binding globulin where it undergoes a series of metabolic changes, specifically (a) the hepatic alteration to a 25-hydroxylated derivative [25(OH)D_3], followed by (b) the renal enzymatic conversion of this derivative to 1,25-dihydroxyvitamin D_3 (Rodan, 1996; Vanderschueren and Bouillon, 1998). 1,25 dihydroxyvitamin D_3 functions to control calcium homeostasis through (a) enhancing the gastrointestinal absorption and renal conservation of calcium, and (b) managing PTH levels (Halloran and Bikle, 1999; Matkovic, 1991;Vanderschueren and Bouillon, 1998). 1,25 dihydroxyvitamin D_3 may also stimulate osteoclastic activity independently of PTH and promote the mineralization of osteoid (Blumsohn and Eastell, 1995).

Given the importance of vitamin D to calcium homeostasis and that VDR is vital for the molecular management of vitamin D action (Christakos, 2002), it is not surprising that the VDR gene is widely scrutinized in osteoporosis studies. Most researchers have focused on a BsmI restriction site polymorphism in the intron separating exons 8 and 9 or a synonymous TaqI polymorphism in exon 9; with their results indicating that the homozygous absence of the BsmI polymorphism and the presence of the closely linked TaqI polymorphism is associated with small reductions in bone mass and increased fracture risk (Cooper and Umbach, 1996; Morrison et al., 1994; Riggs et al., 1995; Wolf et al., 2000). Other researchers, however, have found no association between these variables (Ensrud et al., 1999), suggesting that the effect of these polymorphisms may be mitigated by other factors, specifically differences in calcium intake, body weight and ethnicity (Eisman, 1999; Ferrari et al., 1998; Gennari and Brandi, 2001; Wolf et al., 2000).

2.3.2. "Race"[2]

Researchers have long recognized apparent differences in the accumulation and loss of both bone mass and quality between "black" and "white" populations (Luckey et al., 1989; Pollitzer and Anderson, 1989). For the purpose of this review, I will assume that the racial term "black" refers to those individuals of African descent, while "white" indicates people of European origins. Skeletal differences that occur between these two racial groups include:

(i) Dissimilarities in fetal growth rates – with black fetuses exhibiting greater values for both bone length and weight when compared to white fetuses. This divergence continues into infancy and childhood, with black infants and children demonstrating not only increased skeletal mass and robusticity relative to white infants and children, but also elevated BMD of the midradius, spine and hip (Bell et al., 1991; Pollitzer and Anderson, 1989).

(ii) Differences in the accumulation and loss of BMD - there is consensus among most researchers that black men and women have significantly higher BMD relative to their white counterparts (e.g. Ettinger et al., 1997; Henry and Eastell, 2000; Luckey et al., 1989; Nelson et al., 1995; however, see Solomon, 1979 for an exception). Researchers hypothesize that these increases in BMD may be the result of (a) endocrinological events, such as decreased skeletal sensitivity to PTH in black women (Cosman et al., 1997) and increased growth hormone secretion in black men (Wright et al., 1995); (b) decreased urinary excretion of calcium (Bell et al., 1995; Bell et al., 2001; Luckey et al., 1989); and/or (c) prolonged periods of bone mass accumulation, combined with slower rates of bone loss (Bell et al., 1995; Luckey et al., 1996; Luckey et al., 1989). For example, Luckey and co-workers (1989) found that the white women in their study attained radial peak bone mass between 25-30 years of age; while radial bone density in black women continued to accumulate throughout their fourth and into their fifth decade. Subsequently, Luckey and colleagues (1996) also found that menopausal and post-menopausal bone loss at the radius was approximately twice as rapid in the white when compared to the black women of their study.

(iii) Differences in bone quality - histomorphometric analyses carried out on the iliac crest of black and white men and women demonstrate differences in the trabecular microstructure and histology of bone between the two racial groups (Han et al., 1996;

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[2] Ethnicity is a term which, in many ways, has come to supercede the concept of "race" in the classification of populations (Pollitzer and Anderson, 1989). Whereas race implies categorization based primarily on genetic differences, ethnicity can reflect minute distinctions in group characteristics without necessarily conferring these to a single genetic, cultural or environmental cause (Pollitzer and Anderson, 1989; Villa, 1994a). This conceptual difference becomes extremely important in the study of osteoporosis, as variation in fracture incidence and prevalence may be attributable to multiple, interdependent factors, both genetic and non-genetic (Villa, 1994a). Unfortunately, many researchers obscure this diversity by broadly defining their samples racially, utilizing terms such as "Negro" or "Caucasian" and "black" or "white" (Villa, 1994b). Since this chapter is a literature review, the concept of race, rather than ethnicity, will be discussed.

Schnitzler and Mesquita, 1998). These differences include increased trabecular bone volume and thickness and elevated bone turnover rates in black individuals (Han et al., 1996; Schnitzler and Mesquita, 1998). Assuming that both the resorptive and formative events of the remodeling cycle are balanced, Schnitzler and Mesquita (1998) hypothesize that these elevated turnover rates would lead to rapid replacement of substandard bone, thereby minimizing fatigue damage and non-traumatic fracture risk in these individuals.

In addition to the preceding quality indicators, age-related microstructural changes to trabecular bone also appear to differ between black and white individuals. In their study of 346 iliac crest bone biopsies of South African black and white males and females, Schnitzler and colleagues (1990) discovered that (i) the thickness of individual trabeculae did not decrease in black males over time, (ii) age-associated reductions in trabecular numbers and increases in trabecular separation did not occur in black females, and (iii) the preceding events were found to be reversed in white males and females. These results contrast with those of Han and colleagues (1996), who, instead, found an age associative reduction in trabecular numbers and a corresponding increase in trabecular separation in both the American black and white women of their study.

Despite the intense focus on skeletal differences between individuals of African and European ancestry, researchers are now finding that osteoporotic fracture rates in the latter also exceed those found in individuals of Asian descent (Stini, 1995). Indeed the high female-to-male hip fracture ratio found so prevalently in white Europeans has not been reported in African or Asian populations, where, ironically, the recorded incidence of this specific fracture type among men sometimes exceeds that of women (Maggi et al., 1991). There is, however, considerable heterogeneity in osteoporotic fracture incidence among different African, Asian and European ethnic groups, suggesting a strong non-genetic influence on factors relating to fracture risk in these populations (Fujita et al., 1999; Hu et al., 1993; Johnell et al., 1995; Lau, 1997; Stini, 1995).

2.3.3. Female reproductive history

Several factors occurring during a woman's reproductive life history can positively or negatively affect the accumulation, maintenance and loss of bone, thereby enhancing or minimizing her risk of osteoporotic fracture. These factors include (i) age at menarche, (ii) pregnancy and lactation, and (iii) menopause.

Age at menarche

The majority of cross-sectional studies examining age at menarche and premenopausal bone density indicate that women who experienced early menarche (12.3 - 12.6 years of age) had higher bone density then those who began to menstruate later (13.7- 13.8 years of age) (Ito et a., 1995; Ribot et al.,1992; Rosenthal et al., 1989). Possible explanations for this phenomenon include: (i) an early and continuous exposure to estrogen during growth potentially maximized peak bone mass (Tudor-Locke and McColl, 2000); (ii) an extended period influenced by the protective effects of

estrogen led to increased BMD (Fox et al., 1993; Ito et al., 1995); and (iii) a later age at menarche can be indicative of underlying hormonal abnormalities which, if not corrected (e.g. through the use of oral contraceptives), can result in menstrual irregularities (oligmenorrhea) and amenorrhea - a hypoestrogenic state characterized by increased osteoclastic resorption and decreased osteoblastic function (Kanis, 1996; Schachter and Shoham, 1994; Sowers et al., 1992).

Although convincing, the preceding cross-sectional findings are not universal, with a notable exception originating from the research of Kirchengast and colleagues (1998). In that study, significant relationships between increased body and fat mass indices, but not bone mass, were found in earlier (<12 years) versus moderate (12-14 years) and late (>14 years) maturing individuals. Given these conflicting results, Tudor-Locke and McColl (2000) suggest caution when drawing conclusions concerning the effect of menarcheal age on bone mass.

Pregnancy and Lactation

Pregnancy is characterized by numerous factors that can affect maternal metabolism and facilitate fetal development. These factors include: (i) increased hormonal levels, specifically that of estrogen, serum 1,25-dihydroxyvitamin D_3, PTH and the parathyroid hormone related protein (PTHrP); (ii) augmented intestinal absorption, reduced renal excretion, and mobilization of calcium from the skeleton; and (iii) increased resorption and bone turnover rates, resulting in a loss of bone density (Cross et al., 1995; Kalkwarf and Specker, 2002; Reid, 2002; Ritchie et al., 1998; Tran and Petrovsky, 2002). These effects are particularly profound in the third trimester when increased amounts of calcium (250 mg/day during weeks 35-36) are required for mineralization of the fetal skeleton (Kalkwarf and Specker, 2002).

Despite some of the adverse affects of pregnancy on maternal metabolism, some researchers suggest that the recovery of lost bone density is complete for most women within 12-24 months postpartum (Kalkwarf and Specker, 2002; Phillips et al., 2000). Exceptions include women who become pregnant before 20 years of age (Fox et al., 1993; Sowers, 1996; Sowers et al., 1992), or those that have a pre-existing osteopenic condition that is exacerbated by the metabolic fluctuations of pregnancy (Khastgir et al., 1996; Phillips et al., 2000). Conversely, other researchers have demonstrated that nulliparity can also be associated with low bone density (Fox et al., 1993; Sowers, 1996; Sowers et al., 1992). However, hormonal problems associated with infertility cannot, as of yet, be ruled out as a confounding factor in these findings (Tudor-Locke and McColl, 2000).

Like pregnancy, lactation leads to alterations in maternal metabolism, specifically decreased estrogen and serum concentrations of 1,25 dihydroxyvitamin D_3, increased PTHrP levels, diminished intestinal absorption and renal excretion of calcium, and augmented bone turnover rates and loss, particularly in skeletal sites with a high proportion of trabecular bone (Karlsson et al., 2001; Kalkwarf and Specker, 2002; Reid, 2002; Sowers et al., 1996; Tudor-Locke and McColl, 2000). However, lactation associated fluctuations in bone density do appear to be self-correcting, with recovery linked to the resumption of menses (Kalkwarf and Specker, 1997 / 1995; Polatti et al.,

1999; Sowers, 1996). This recovery usually occurs in most women 18-24 months postpartum and is not significantly enhanced by calcium supplementation or adversely influenced by a successive pregnancy (Kalkwarf et al., 1997; Polatti et al., 1999; Sowers et al., 1996; Tudor-Locke and McColl, 2000).

Menopause

Menopause refers to the permanent cessation of menstruation and usually occurs in women around 50 years of age, with median ages between 40-50 widely reported (Brincat et al., 1991; Pavelka and Fedigan, 1991). Physiological changes associated with menopause include: (i) reduced levels of circulating estrogen, promoting increased secretion of interlukin-6 and other osteoclast-recruiting cytokines; (ii) augmented rates of osteoclastic resorption, leading to suppression of the parathyroid gland, and; (iii) diminished PTH levels, resulting in reduced production of 1,25 dihydroxyvitamin D_3 and subsequent decreases in the intestinal absorption of calcium (Marcus, 1994). These menopausal changes precipitate the reduction of bone mass (Lindsay, 1995; Nilas and Christiansen, 1986) and adversely alter the microarchitecture of trabecular bone, specifically at the vertebrae and wrist, through the resorption of individual trabeculae and the loss of inter-trabecular connectivity (Dempster et al., 1986).

2.3.4. Lifestyle factors

2.3.4.1. Diet

The human skeleton is a composite material consisting of both organic and inorganic components. These components are constructed from a vast array of dietary constituents, specifically protein, vitamins and minerals, with each affecting the way in which the body deposits and sustains genetically pre-determined complements of bone (Heaney and Matkovic, 1995). Of these constituents, calcium is deemed essential for the maximization and maintenance of peak bone mass and quality (Heaney, 2002; Heaney and Matkovic, 1995). Adequate calcium intake during growth will maximize peak bone mass, providing greater latitude for the maintenance of skeletal integrity during the onset of age associated bone loss (Goulding et al., 1998; Hu et al., 1993(a); Matkovic, 1991; Sandler et al., 1985). Additionally, an adequate intake of calcium ensures proper cortical thickness and trabecular connectivity and numbers, thereby enhancing skeletal rigidity (Heaney and Matkovic, 1995).

In addition to its formative functions, calcium is also involved in most metabolic processes of the human body. To regulate these processes, serum calcium concentration is narrowly limited (range 2.1 to 2.6 mmol/L), with any fluctuations in these limits controlled by PTH, vitamin D and calcitonin (Nieves, 2002). Produced by the parathyroid, thyroid and thymus glands, calcitonin is recognized as an "anti-resorptive" peptide hormone that inhibits extracellular Ca^{2+} sensing and minimizes osteoclastic resorption (Zaidi et al., 2002). Any calcium that is not required for immediate metabolic functioning is stored in the skeleton, where up to 99% of the body's calcium is amassed, and drawn upon in times of need (Nieves, 2002).

Whereas an adequate daily intake of calcium is necessary to maximize metabolic and skeletal health, sufficient retention and minimal loss of the mineral is also required to normalize the balance of calcium within the body (Nieves, 2002). Unfortunately, calcium retention in the adult human is relatively inefficient, with only 4-8% of ingested calcium being absorbed (Heaney and Matkovic, 1995). While this rate is higher among infants, children and adolescents, retained calcium is continually being turned over in order to maintain normal serological levels and extracellular functions (Heaney and Matkovic, 1995; Stini, 1990). This dynamic nature is such that many factors can alter calcium homeostasis and produce either a positive or negative calcium balance (Stini, 1990). Endocrinological events, such as decreases in PTH and vitamin D, can reduce intestinal/renal absorption thereby augmenting the urinary and fecal excretion of calcium (Charles et al., 1991). Dermal loss through sweating also contributes to the serological decline of calcium and this, when combined with the preceding endocrinological events, can result in reduced concentrations of calcium in the extracellular fluids (Charles et al., 1991; Matkovic, 1991). Although osteocytic osteolysis facilitates calcium diffusion in and out of bone (Nijweide et al., 2002; Shipman et al., 1985), these reductions in fluid calcium levels can also be compensated for by increased osteoclastic activity (Stini, 1990).

In addition to the aforementioned physiological processes, excessive consumption of several other dietary constituents can adversely affect calcium homeostasis by altering the absorption or obligatory excretion of this mineral (Heaney et al., 2000). Some of these constituents are noted in Tables 2.3(a) and 2.3(b).

2.3.4.2. Cigarette smoking

Whereas numerous studies have linked tobacco use with lower levels of bone acquisition in adolescents (Välimäki et al., 1994), and decreased BMD and greater risk of fracture in adults (Forsén et al., 1994; Jones and Scott, 1999; Krall et al., 1991; Law and Hackshaw, 1997; Ortego-Centeno et al., 1997 ; 1994), others have found no association (Daniel et al., 1992; Fehily et al., 1992). These inconsistencies are likely attributable to the range of tobacco usage noted in these studies and other confounding variables that are commonly present in individuals who smoke (e.g. increased use of alcohol and decreased physical activity levels) (Cooper et al., 1992; Ganry et al., 2000; Heaney et al., 2000; Ortego-Centeno et al., 1997). Despite these contradictions, however, heavy tobacco usage has been positively associated with several consequences that can adversely affect skeletal health in women. These consequences include: (i) increased risk of oligomenorrhea, (ii) premature menopause, (iii) diminished neuromuscular function (specifically decreased muscular strength and coordination), and (iv) decreased body / fat mass, which results in (v) decreased peripheral production of estrogens and (vi) reduced load bearing weight on the skeleton (Adami and Braga, 1998; Hartz et al., 1987; Jensen et al., 1985; Nelson H. et al., 1994). The mechanism by which smoking influences skeletal health in males is not yet clearly elucidated, although factors such as the level of physical activity are thought to be implicated (Ortego-Centeno et al., 1997).

2.3.4.3. Physical activity levels and body weight

Bone is constantly changing, remodeling its mass, external geometry and internal microarchitecture to adapt to mechanical loads (Beck and Marcus, 1999). These loads, which are a function of weight bearing activity, are characterized by several variables including: (i) peak load magnitude, (ii) the number of load cycles, (iii) the rate of strain (or the time during which bone undergoes proportional changes in length due to loading or impact), and (iv) the type of load (Beck and Marcus, 1999; Currey, 2001; Lanyon, 1984; Marcus, 1996). Alterations in the extent of these variables will, hypothetically, initiate a sequence of cellular events, beginning with the biochemical perception and translation of load induced stimuli and ending with site-specific adjustments to the remodeling rate (Lanyon, 1984). Several investigators suggest that these preliminary biochemical functions are performed by the osteocyte (Martin, 2000; Mullender et al., 1998).

Commonly assumed to be the skeletal system's mechanosensory cell, the osteocyte senses the application of mechanical loads, possibly by way of stress generated fluid flows within the canaliculae (Cowin et al., 1995; Marcus, 1996; Turner et al., 1995; Weinbaum et al., 1994) or electrical potentials (Harrigan et al., 1993; O'Connor et al., 1982), and produces a cellular signal proportional to said load (Cowin et al., 1995; Marotti et al., 1992). This assumption is substantiated by evidence demonstrating that osteocytes: (i) respond metabolically to applied mechanical loads (Mason et al., 1996), (ii) have receptors for both PTH and estrogen (Mason et al., 1996) and (iii) are able to communicate not only with one another, but also with osteoblastic bone lining and bone forming cells, modulating their activity through the use of electrical signals and gap junctions (Marotti et al., 1992; Mason et al., 1996; Shirrmacher et al., 1992; Yamaguchi et al., 1994). Turner and colleagues (1995) suggest that it is the osteoblastic bone lining cell that receives signals from the osteocyte and ultimately activates the remodeling sequence in response to increasing or decreasing loads on the skeleton. When bone is subjected to optimal (peak) loading, nearby BRUs modulate their cellular endeavours, depositing new bone onto existing surfaces and decreasing osteoclastic activity (Lanyon, 1984; Heaney and Matkovic, 1995; Marcus, 1996). However, when load magnitudes decrease below optimal thresholds, deposition rates are decelerated or even arrested, resulting in a reduction of bone mass through the relative increase in osteoclastic resorption (Marcus, 1996).

Whereas the number of load cycles minimally influence bone density values when less than optimal load magnitudes are applied (Heinonen et al., 1995; Kerr et al., 1996; Robinson et al., 1995; Whalen et al., 1988), the rate of strain has been shown to be critical in the skeletal response to mechanical loading, specifically in terms of bone formation and mineral apposition rates (Beck and Marcus, 1999; Turner et al., 1995). Repeatedly, researchers have demonstrated that augmented strain rates created by the application of heavy loads and/or high impact forces (i.e. weightlifting and/or gymnastics), can increase BMD in the skeletal areas to which the load or force is applied (Heinonen et al., 1995; Nelson M. et al., 1994; Robinson et al., 1995). In contrast, low-impact activities and light to moderate loading of the skeleton do not lead to significant adaptive improvements in adults (Forwood, 2001; Forwood and Burr,

1993; Kerr et al., 1996). Nonetheless, these forms of exercise are frequently recommended for both children and elderly individuals, as they can lead to significant increases in BMD in the cortical and trabecular moieties (Forwood and Burr, 1993; Slemenda et al., 1994) of the former, and improve overall fitness, coordination and muscular strength in the latter, thereby minimizing their risk of falling and fracture (Nelson M. et al., 1994; Wickham et al., 1989).

Although many cross-sectional studies indicate that habitual physical activity, typified by high impacts and heavy loads, are beneficial for the male skeleton, excessive exercise in females may actually lead to decreased bone density (Marcus, 1994; Stini, 1995). This decrease is associated with the severe reduction in weight found in highly athletic women (Snead et al., 1992). Body weight, specifically lean muscle and fat mass, has been found to be a very powerful determinant in both the attainment and maintenance of peak bone mass (Heaney and Matkovic, 1995; Slemenda et al., 1994). Excessively low body weight leads to a reduction in the mechanical loads borne by the skeleton (Heaney and Matkovic, 1995), a decrease in the circulating levels of PTH, thereby minimizing the tubular reabsorption of calcium and the renal production of 1,25 dihydroxyvitamin D_3 (Bell et al., 1985), and a loss of menstrual regularity resulting in estrogen-dependent bone loss (Drinkwater et al., 1990; Kalkwarf and Specker, 1995; Schachter and Shoham, 1994). Consequently, the skeletal density of women, unlike that of men, may not benefit from extreme levels of physical activity (Snead et al., 1992). This risk is, perhaps, greatest among female elite athletes who have yet to achieve their peak bone mass.

2.4. CONCLUSIONS

Osteoporosis is a heterogeneous disorder, characterized by low bone mass and microarchitectural deterioration of osseous tissue, resulting in severe skeletal atrophy, compromised skeletal strength, and an increased occurrence of non-traumatic fractures (Avioli and Kleerekoper, 1998; Kanis, 1996; Ross, 1998). Clinically categorized into primary or secondary forms, osteoporosis can afflict both men and women, with fractures predominating in areas of trabecular bone (Kholsa et al., 1995; Lindsay, 1995; Melton, 1995; Stini 1995). Causal contributors, or risk factors, associated with the onset and/or progression of this disease include: increasing age, genetic predisposition, race, female reproductive factors, and a bevy of lifestyle choices, specifically dietary intake, cigarette smoking, levels of physical activity and body weight.

Table 2.1. The pathophysiological characteristics associated with types I and II involutional osteoporoses

Characteristics	Type I	Type II
Classification	"post-menopausal"	"senile"
Age at fracture onset	51-75 years of age	> 70 years of age
Sex ratio (F:M)	6:1	2:1
Type of bone loss	**osteoclast** mediated bone loss: • ↑ resorption rates in trabecular areas • ↑ activation frequencies • deeper resorption cavities • perforation and disconnection of trabeculae • trabecularization of cortical bone on the endosteal surface	**osteoblast** mediated bone loss: • fewer osteoblasts resulting in a ↓ in bone formation • shallower formation • ↓ activation frequencies • thinning of trabeculae and cortex of long bones
Rate of bone loss	accelerated	prolonged
Fracture types	• vertebral crush fractures • Colles' fractures of distal radius • fractures of the ankle • endentulism due to excess loss of perialveolar bone	• vertebral wedge fractures • hip fractures • fractures of proximal humerus and tibia • fractures of the pelvis
Causal mechanisms	factors related to **menopause**: • ↓ in estrogen, leading to: ↑ production in the bone-resorbing cytokines in IL-1, IL-6, and TNF ↑ in bone resorption ↑ in plasma calcium levels ↓ in PTH secretion ↓ in 1,25 $(OH)_2D_3$ production ↓ in calcium absorption ↑ in renal calcium excretion	factors related to **aging**: • ↑ PTH secretion, leading to: ↑ calcium mobilization from the skeleton ↓ mineral content of bone • ↓ in the absorption of $1,25(OH)_2D_3$ • ↓ 1,25 $(OH)_2D_3$ production • ↓ in calcium absorption

(Hock et al., 2002; Kholsa et al., 1995; Melton, 1995; Riggs and Melton, 1986; 1983; Stini, 1990)

Table 2.2.(a). Selected secondary causes of osteoporosis

Pathogenic / Contributory Factors	
• **Connective tissue disorders:** Osteogenesis imperfecta **(Stini, 1990)** genetic mutations in type I procollagen • **Endocrine disorders:** Diabetes mellitus **(Kholsa and Melton, 1995)** ↓ osteoblast function ↑ renal loss of calcium Hypogonadism **(Reid and Harvey, 1997)** ↓ osteoblast function ↑ bone turnover ↓ peak bone mass Hyperparathyroidism **(Davies, 1999)** ↑ bone turnover ↑ bone resorption Hyperthyroidism **(Davies, 1999; Kholsa and Melton, 1995)** ↓ PTH and 1,25-dihydroxyvitamin D_3 ↑ numbers of BRUs ↑ bone resorption • **Gastrointestinal disorders:** Malabsorption **(Davies, 1999; Kholsa and Melton, 1995)** ↓ bone mass ↓ absorption of calcium ↓ absorption of vitamin D	• **Psychiatric illness:** Anorexia nervosa **(Hay et al., 1992; Reid and Harvie, 1997; Rigotti et al., 1984)** Amenorrhea ↓ body weight ↑ cortisol levels • **Rheumatic Diseases:** Rheumatoid arthritis **(Reid and Harvie, 1997; Stini, 1990)** ↑ production of glucocorticoids ↑ bone resorption ↓ physical activity levels due to ↓ mobility Ankylosing spondylitis **(Çakir et al., 2002; Maillefert et al., 2001; Reid and Harvie, 1997)** systematic inflammation ↑ cytokine activity ↑ bone resorption

Table 2.2.(b). Selected secondary causes of osteoporosis

Iatrogenic / Contributory Factors
• **Drug –induced:** Anticonvulsants (including phenytoin, phenobarbitone, carbamazepine and sodium valproate) **(Melton et al., 1999; Scane et al., 1999)** ↓ bone density ↑ vertebral fractures Corticosteroids **(Kholsa and Melton, 1995; Reid and Harvie, 1997; Stini, 1990)** ↓ osteoblast function ↑ bone resorption ↓ calcium absorption ↑ urinary excretion of calcium + corticosteroids adversely affect cytokines and bone growth factors Diuretics **(Stini, 1990)** ↑ urinary excretion of calcium • **Immobilization (Proctor et al., 2000)** ↓ muscle-induced strains on the bone ↓ in bone mineral density • **Surgeries:** Oophrectomy **(Reid and Harvie, 1997)** ↓ in estrogen ↑ bone resorption ↓ PTH Organ transplants (kidney, heart, liver and lung) **(Reid and Harvie, 1997)** ↑ in bone turnover ↓ in BMD

Table 2.3(a). Selected dietary constituents and their effects on skeletal health

Constituent	Effects on skeletal health	References
Alcohol	**chronic intake** (> 100g / day) results in: • ↑ risk of falling / skeletal trauma • ↓ PTH • ↑ urinary excretion of calcium • ↓ serum levels of vitamin D metabolites • ↑ bone resoprtion and ↓ bone formation **moderate intake** (15-30 g / day) results in: • higher bone mass at trochanter and spine • ↓ in fracture rates in both ♀ and ♂	**Cheung et al., 1995; Diamond et al., 1989; Diéz et al., 1994; Ganry et al., 2000; Heaney et al., 2000; Holbrook and Barrett-Connor, 1993; Johnell et al., 1995; Krõger et al., 1994, Laitinen et al., 1992; New et al., 1997; Pepersack et al., 1992; Stini, 1995**
Animal Protein	**excessive intake** results in: • ↑ acid secretion by the kidneys to catabolize proteins → release of calcium from the skeleton to act as a buffer • ↑ urinary excretion and ↓ renal reabsorption of calcium • ↓ accumulation of bone mass → ↑ fracture risk **inadequate intake** result in: • ↓ IGF-1 levels, immunity and muscle function • ↑ risk of falling and fracture (especially in elderly)	**Abelow et al., 1992; Hu et al., 1993(b); Marsh et al., 1988; Munger et al., 1999; Nieves, 2002**
Caffeine	**excessive intake** (e.g. > 2 cups per day) results in: • ↑ urinary excretion of calcium • ↑ bone loss and fracture rates above problems may only occur in the absence of adequate calcium intake	**Cooper et al., 1992; Harris et al., 1994; Hernandez-Avila et al., 1991; Kiel et al., 1990; Nieves, 2002; Picard et al., 2000; Stini, 1995**
Fibre	**excessive intake** results in: • ↑ intestinal bulk → ↓ transit time for calcium absorption • chelation and ↑ fecal excretion of calcium	**Stini, 1990**

Table 2.3(b). Selected dietary constituents and their effects on skeletal health (continued)

Constituent	Effects on skeletal health	References
Phosphorus	**excessive intake** (when combined with a low calcium-to-phosphorus ratio) results in: • ↑ PTH production and ↑ urinary excretion of calcium • ↑ bone resoprtion and ↓ BMD in girls and young adult ♀ • ↑ fracture rates in girls	**Calvo et al., 1990; Heaney et al., 2000; Neville et al., 2002; Wyshak and Frisch, 1994; Wyshak et al., 1989**
Sodium	**increases** of 100 mmol / day over average intake (e.g. 70-250 mmol / day) results in: • ↑ daily excretion of 0.6 – 1.5 mmol of calcium (although the relationship is likely not linear) • ↑ PTH production, osteoclastic resoprtion and bone loss • ↑ urinary excretion of hydroxyproline (a marker of bone collagen degradation and bone turnover)	**Adami and Braga, 1998; Cohen and Roe, 2000; Devine et al., 1995; Evans and Eastell, 1995; Heaney et al., 2000; Itoh and Suyama, 1996; Matkovic et al., 1995; Nordin et al., 1993; Yano et al., 1985**
Vitamin D	**severe deficiency** results in: • secondary hyperparathryoidism • ↓ acquisition of bone during growth and • ↓ calcification of osteoid tissue • ↑ bone turnover and ↓ bone mass • rickets (children) / osteomalacia (adults) **insufficiency** results in: • ↓ intestinal absorption and ↑ renal excretion of calcium • ↑ serum PTH production and bone resorption	**Chapuy et al., 1997; Dagnelie et al., 1990; Docio et al., 1998; Halloran and Bikle, 1999; Heaney et al., 2000; Matkovic, 1991; Thomas et al., 1998; Vanderschueren and Bouillon, 1998**

Page 27 has been removed due to copyright restrictions. The information removed was Figure 2.1 (a-f) (The processes of skeletal remodeling. de Vernejoul, 1998:3)

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CHAPTER THREE: BONE LOSS AND OSTEOPOROTIC FRACTURE PREVALENCE IN PAST POPULATIONS

3.1. INTRODUCTION: THE PALEOPATHOLOGICAL EXAMINATION OF BONE LOSS

Osteopenia is an all-inclusive term referring to bone loss without fracture development (Ross, 1998). Osteoporosis is also characterized by bone loss, specifically substantial decreases in skeletal quantity [i.e. bone mineral content (BMC) and/or mineral density (BMD)] and quality (Avioli and Kleerekoper, 1998; Brickley, 2000). These decreases result in severe skeletal atrophy, compromised skeletal strength, and an increased occurrence of non-traumatic fractures in both men and women (Avioli and Kleerekoper, 1998; Kanis, 1994; Ross, 1998). Currently, it is estimated that 1.4 million Canadians suffer from osteoporosis; one in four women and one in eight men over fifty years of age will eventually develop this disease, resulting in medical expenditures in excess of 1.3 billion dollars per year (Osteoporosis Society of Canada, 2003). Given these estimates, it is evident why the study of bone loss and osteoporosis within a clinical setting is of vital importance to the long-term health and welfare of ageing populations. For the bioarchaeologist, however, the question lingers as to whether the paleopathological examination of bone loss and subsequent osteoporotic fracture can provide relevant data concerning the etiological processes and patterns of this common "modern-day" disorder (Weaver, 1998).

Although it is widely acknowledged that increasing age, alterations in hormone levels (specifically those associated with menopause), and genetic predisposition causally contribute to osteoporosis (Deng et al., 2000; Riggs and Melton, 1986; Schnitzler, 1993), several extrinsic factors are also known to augment an individual's fracture risk (Mays, 1998). These factors, which include the detrimental intake of specific dietary nutrients (Heaney and Matkovic, 1995), the excessive consumption of alcohol (Heaney et al., 2000; Stini, 1995) and cigarettes (Jones and Scott, 1999; Krall et al., 1991), and decreased physical activity levels (Marcus, 1996), are frequently associated with the modern-day lifestyle. Given that the primary goal of paleopathological inquiry is to situate within a historical context information concerning the physiological adaptations of the human skeleton to stress (Agarwal and Grynpas, 1996; Ortner, 1991; Ubelaker and Grant, 1989; Walker, 2000), numerous researchers have tested the association between lifestyle and patterns of bone loss and fracture prevalence in individuals who maintained ways of life very different from those of modern day people (see tables 3.1[a] - 3.3). However, as with all paleopathological investigations, there are many limitations associated with the analysis of bone loss and osteoporosis in archaeological skeletal remains.

3.2. LIMITATIONS ASSOCIATED WITH THE PALEOPATHOLOGICAL ANALYSIS OF BONE LOSS AND OSTEOPOROSIS

Conventional diagnosis of both osteopenia and osteoporosis is dependent upon the identification of decreased bone quantity and/or quality. Current clinical methods

used in the diagnosis of these disorders include quantitative ultrasound (Kanis et al., 1999), computed tomography (Gordon et al., 1998; Haidekker et al., 1999), dual energy x-ray absorptiometry (Adachi, 2000; Zmuda et al., 2000), and a variety of histomorphometric techniques (Legrande et al., 2000; Vesterby, 1993), with many of these methods being applied to ancient and historic skeletal remains. Unlike clinicians, however, bioarchaeologists are faced with several limitations that could adversely skew the results and, ultimately, the interpretations of their findings. These limitations include problems of paleodemographic inference and post-mortem diagenesis.

3.2.1. Problems of paleodemographic inference

Paleodemography is an often contentious field of anthropological study which, through the use of sampled archaeological data, (i) estimates the distribution, density, age and sex structures of past populations and (ii) postulates and answers theoretical questions concerning the rates of growth and decline experienced by these groups (Chamberlain, 2000; Meindl and Russell, 1998). To do this, paleodemographers, like paleopathologists, interpret their data through the use of inference, or the presupposition that statistical information generated from archaeological skeletal samples can accurately reflect the life history of populations from which the samples came (Wood et al., 1992). This underlying presupposition has led to severe criticism of both fields of study, beginning with the critique postulated by Peterson (1975), and followed by those of Bocquet-Appel and Massett (1982) and others. These critiques have focused on methodological issues, specifically problems associated with:

(i) Accurate age estimation – age at death estimates are based upon a uniformitarian assumption, one which states that the biological relationship between age and specific morphological indicators of skeletal ageing is constant across populations and over time (Chamberlain, 2000; Hoppa, 2000). Given this premise, age estimates and their associated ranges of error are obtained by observing changes in one or more morphological indicators in an archaeological sample and comparing these changes to similar alterations noted in a reference population of known age, sex, and, preferably, biogeographic origin (Chamberlain, 2000). However, skeletal ageing is a multi-faceted process, one in which inter- and intra-individual variability increases dramatically from the third decade of life on (Meindl and Russell, 1998). This variability augments the inaccuracy and bias associated with the various methods of age estimation, and can skew the age ranges of the archaeological sample to reflect those of the selected reference population (Buikstra and Konigsberg, 1985; Meindl and Russell, 1998; Saunders et al., 1992).

(ii) Accurate sex determination – the determination of sex within a paleodemographic context is dependent upon (a) the magnitude of sexual dimorphism between males and females within a population and (b) the amount of within-sex variation (Meindl and Russell, 1998). Thus sex determination, like age estimation, is very group specific and, depending upon the method employed, requires the selection of an appropriate reference population to minimize inaccuracy and bias (Meindl and

Russell, 1998). The most reliable indicators of sex in adult skeletons are those dimorphic characteristics of the innominate bone, specifically attributes of the subpubic region (e.g. the ventral arc, the subpubic concavity, and the ischiopubis ramus ridge), the greater sciatic notch, and the periauricular sulcus (Buikstra and Ubelaker, 1994). Unfortunately, these attributes are not always recovered in an archaeological context, necessitating the use of less reliable skeletal features, such as those found on the cranium. However, the use of cranial attributes to the exclusion of all other sex indicators has led to an over-representation of males in archaeological samples (Meindl et al., 1985; Milner et al., 2000; Walker, 1995). This is likely caused by the overlapping distribution of cranial features between the sexes and the "masculinization" or increased robusticity of these features in older females (Meindl et al., 1985; Milner et al., 2000; Ruff, 1981; Walker, 1995).

(iii) Sampling issues – it has long been recognized that skeletal collections are inherently biased cross-sectional samples of past individuals from any given age range (Milner et al., 2000). Some of these biases are conceptual in nature, focusing on problems of:

a) demographic nonstationarity – or the departure of a population from a stationary state (Wood et al., 1992). Assumptions commonly associated with stationary populations include closed migration, extended periods of unaltered fertility and mortality, zero growth rates, and stable age distributions (Milner et al., 2000). However, since few real life populations experience all of these underlying assumptions, problems of demographic nonstationarity arise, resulting in mean age-at-death estimations that reflect changes in fertility rather than mortality (Jackes, 1993; Johansen and Horowitz, 1986; Milner et al., 2000; Sattenspiel and Harpending, 1983).

b) hidden heterogeneity – or the often immeasurable susceptibility of each individual within a population to disease and death (Wood et al., 1992). This susceptibility, or frailty, is highly heterogeneous and is dictated by many factors, including genetic predisposition to certain diseases and exposure to detrimental social, economic, and/or environmental conditions (Milner et al., 2000; Wood et al., 1992; Vaupel, 1990). Since this heterogeneity may be hidden (or not captured adequately by measurable variables), the risk of morbidity and mortality experienced by each individual within an aggregate may not be representative of the rates of morbidity and mortality experienced by the aggregate as a whole (Milner et al., 2000). This discontinuity between individual risk and aggregate rates of morbidity and mortality would, of course, compromise any inferences concerning the health status of past populations.

c) selective mortality – rather than supplying data on all age-specific individuals who were at risk of disease and/or death in a population, archaeological skeletal samples provide information only on those select individuals that died in each age category (Wood et al., 1992). Since individuals in these samples are more

> likely to exhibit pathological lesions that either increased their risk of dying or causally contributed to their death, any use of statistical inference would likely overestimate lesion frequency in parent populations and, once again, bias any interpretations of past health (Milner et al., 2000; Wood et al., 1992).

Other sampling biases pertain to taphonomic factors, specifically the differential treatment, deposition, excavation and curation of archaeological skeletal remains; these factors are all influenced by the post-mortem effects of diagenesis (Milner et al., 2000).

3.2.2. Problems of post-mortem diagenesis

Diagenesis is a term which encompasses all physical, chemical or biological processes that alter the organic and inorganic constituents of bone within the burial environment (Hedges and Millard, 1995a; Lyman, 1994)[1]. The affects of these processes are highly variable and are dependent upon (i) factors intrinsic to the skeleton, i.e. the size, porosity, and chemical structure of osseous elements, and (ii) extrinsic factors unique to each interment site (Hanson and Buikstra, 1987; Lyman, 1994). Examples of the latter include the hydrology (Hedges and Millard, 1995a), soil pH (Hedges and Millard, 1995a; Neilsen-Marsh et al., 2000) and plant, fungal and microbial composition of the burial milieu (Child, 1995; Hanson and Buikstra, 1987; Nielsen-Marsh et al., 2000). Taking into account the intrinsic characteristics of osteopenic/osteoporotic bone, specifically the decreased bone mineral content and diminished micro-architectural integrity of the tissue, it is likely that these extrinsic factors would accelerate the post-burial disintegration of osteopenic/osteoporotic remains thereby distorting the paleopathological reconstruction of these disorders (Walker, 1995). For those remains that are recovered, however, distinguishing the effects of diagenesis from those processes of a pathological nature can also prove to be problematic (Agarwal and Grynpas, 1996). Although diagenetic modifications are recognizable through histological changes in tissue porosity, collagen content, crystallinity and/or the presence of exogenous ions, the extent of modification is often difficult to determine with any degree of absolute certainty (Brickley and Howell, 1999; Farquharson and Brickley, 1997; Hedges and Millard, 1995b; Nielsen-Marsh et al., 2000). Diagenesis may also minimize the efficacy with which some diagnostic techniques, specifically radiography, dual energy x-ray absorptiometry and histology, are used in the paleopathological evaluation of bone loss (Kneissel et al., 1994; Mays, 1996; Mays et al., 2001; Stout, 1978; Weaver, 1998).

Despite the limitations associated with paleodemographic inference and taphonomic factors, the use of appropriate archaeological skeletal samples can be very advantageous in the paleopathological study of bone loss and fracture. Archaeological populations are commonly assumed to be more homogeneous, both genetically and in terms of lifestyle factors (i.e. diet and behavior), when compared to modern groups (Cho, 2002; Rewekant, 1994; Ruff and Hayes, 1983). If this assumption is correct, the homogeneity of these populations can facilitate the examination of multi-faceted disorders such as bone loss, and provide insight into the specific biocultural aspects of

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[1] Please note that similar diagenetic processes operate on the organic and inorganic constituents of teeth.

these conditions (Agarwal and Grynpas, 1996; Dequeker et al., 1997; Mays, 1998). This insight can aid not only in the reconstruction of past health patterns, a central tenet of any paleopathological investigation, but also provide information facilitating the generation of hypotheses prior to testing in a clinical setting (Pfeiffer and Lazenby, 1994). In this way, the paleopathological investigation of osteopenia and osteoporosis can provide relevant data concerning the etiological processes and patterns of this modern-day disorder.

3.3. BONE LOSS AND OSTEOPOROSIS IN THE ARCHAEOLOGICAL RECORD

The study of bone loss in the archaeological record has been conducted in many biogeographically diverse populations, including individuals from Europe, North America, Egypt and Sudanese Nubia. These examinations have employed various diagnostic techniques, both invasive (e.g. histomorphometry and cross-sectional measurement) and non-invasive (e.g. photon absorptiometry and microradiography) to measure the loss of bone quantity and quality in the past (Agarwal and Grynpas, 1996). For a listing of these studies, including information on sample and methodologies used, please refer to Tables 3.1(a) through to Table 3.3 at the end of this chapter.

3.3.1. Cortical bone loss

Skeletal evidence of cortical bone loss in the archaeological record can be encapsulated by the following three "trends". The first is one of progressive cortical bone loss after the attainment of peak bone mass and with advancing age (Carlson et al., 1976; Cho, 2002; Mays et al., 1998; McEwan et al., 2004; Perzigian, 1973). This loss differentially occurs in both men and women, resulting in decreased cortical mass. For example, Carlson and colleagues (1976) found significant decreases in the femoral cortical area and thickness of older (41-55 years) relative to younger (20-40 years) individuals in their Amerindian sample. These decreases were more pronounced in the females when compared to that of the males. Similar findings were also noted by Cho (2002) in her study of an Imperial Roman cemetery sample. Examination of the rib and femur revealed age-associated decreases in cortical mass, which Cho (2002) attributed to declining cortical area measurements coupled with increased intra-cortical porosity and endosteal expansion. Cortical bone loss was, once again, greater in the females when compared to the males of her sample.

Other researchers examining biogeographically and temporally diverse groups from Europe (Drusini et al., 2000; Mays, 2000; 1996; Mays et al., 1998; Rekewant, 1994), North America (Ericksen, 1980; 1976; Gunness-Hey, 1987; Perzigian, 1973; Ruff and Hayes, 1983), and Sudanese Nubia (Martin and Armelagos, 1979) have also reported comparable findings of age-associated declines in cortical bone, losses which are consistently larger in females and are manifested by way of decreased cortical mass and histomorphometric measurements. The universality of these results would suggest that age-associated bone loss in not a temporally or culturally specific phenomenon.

However, an exception to this apparent trend is noted in the findings of Ekenman and colleagues (1995).

Through the use of radiography, single energy scanning and dual photon absorptiometry, Ekenman and colleagues (1995) examined the humerus, radius, second metacarpal, femur and tibia of 241 individuals (187 males, 156 females) from a Stockholm medieval cemetery site. Although thinner cortices of the upper extremities were recorded relative to contemporary reference scores, an absence of age associated bone loss in the older individuals (> 40 years) of either sex and increased diaphyseal bone mineral density (BMD) of the femur and tibia were observed. High levels of physical activity, specifically during periods of growth and throughout adulthood, are considered by these authors to be a contributory factor in the preservation of BMD in this sample.

The second trend is one of decreased cortical mass in women, both absolutely and relatively, when compared to that of men, with sex differences most apparent in the femur (Carlson et al., 1976; Cho, 2002; Dewey et al., 1969; Martin and Armelagos, 1979; 1985; Rekewant, 1994; Ruff and Hayes, 1983; Ruff et al., 1984; Thompson and Gunness-Hey, 1981; Thompson et al., 1981; Van Gerven et al., 1969). This discrepancy is likely attributable to the differential rates of skeletal remodeling that occur in men versus women. For example, Martin and Armelagos (1979; 1985) found that the females of their Sudanese Nubian samples (350 BC – AD 1300), specifically those in the 20-29 age category, exhibited increased numbers of resorption spaces and forming osteons (which are indicative of slow bone mineralization rates) and augmented bone turnover rates when compared to that of the males. Subperiosteal bone apposition, a remodeling mechanism which compensates for the rapid age-related resorption of endocortical bone, was also found to be deficient in Native American (Carlson et al., 1976), Sudanese Nubian (Dewey et al., 1969), and Roman (Cho, 2002) women when compared to that of the men. Extrinsic factors that may contribute to the differential rates of cortical bone remodeling and loss between the sexes of these populations include: (i) gender specific activities and activity levels (Burr et al., 1990; Cho, 2002; Erickson, 1976; Ruff and Hayes, 1983), (ii) disparities in the intake of calcium and protein (Pfeiffer and King, 1983), and (iii) dietary deficiencies exacerbated by the stress of pregnancy and lactation (Dewey et al., 1969; Martin and Armelagos, 1979; 1985, however see Erickson, 1976 for critique of this hypothesis).

The third trend is one of similarity, with archeological patterns of cortical bone loss broadly emulating the cortical reduction found in select contemporary populations (Mays, 2000; 1996; Van Gerven, 1969). For example, Mays found a comparable age-related decline in measurements of cortical index [2] in both historical (2000) and medieval (1996) British samples when compared to a modern Finnish population. Fractures were present in both archaeological samples, although not all could be symptomatically linked to excessive cortical bone loss. In the former, a historical cemetery sample from Spitalfields, London, England (AD 1732-1849), rib fractures

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[2] As stated by Mays (1996), cortical index is a measurement of thickness, specifically the percentage of bone width taken up by the cortex, and is calculated as:

$$\text{cortical index} = \frac{\text{total bone width} - \text{medullary width}}{\text{total bone width}} \times 100$$

predominated and were not significantly correlated to cortical index measurements of the second metacarpal. In contrast, a statistically significant association between low cortical bone indices of the second metacarpal and rib and vertebral fractures were found in individuals from the medieval peasant sample of Wharram Percy (Yorkshire, England AD 10^{th}-16^{th} C). This association was significant only in the females and did not occur with fractures other than those of the ribs and vertebrae. Findings of appendicular cortical bone loss associated with fractures of highly trabecular sites in the axial skeleton have also been recorded in modern clinical populations (Seely et al., 1991; Wishart et al., 1993). This similarity calls into question the role of lifestyle factors in osteoporotic fracture risk (Mays, 1996).

In clinical literature, lifestyle factors such as adequate levels of weight-bearing activity (Heinonen et al., 1995; Robinson et al., 1995), optimum intake of dietary calcium and vitamin D (Halloran and Bikle, 1999; Nieves, 2002), and avoidance of detrimental substances such as tobacco (Jones and Scott, 1999), are thought to promote bone health thereby reducing the risk of osteoporotic fracture. Given the characteristics of rural life at Wharram Percy, it is likely that many of these positive lifestyle factors would have been practiced amongst the peasant community. Both Derevenski (2000) and Mays (1996) state that labor intensive activities, including plowing, gardening, dairying, and spinning and weaving, would have been a daily norm for these individuals. Adequate levels of calcium and vitamin D are also assumed given that: (i) the site is located on chalk geology and high levels of calcium would have been found in the local water system and food chain, and (ii) vitamin D deficient diseases, such as osteomalacia and healed rickets, were not found among the adult skeletons (N=358) (Mays, 1996). Finally, cigarette smoking would not have been an issue, as tobacco was not available in England at this time (Mays, 1996). However, despite living a life that should promote bone health, the study conducted by Mays (1996) demonstrates that the post-menopausal women of Wharram Percy experienced comparably modern rates of bone loss leading to osteoporotic fractures. What appears to be different is the location of these breaks, with hallmark fractures of the hip and wrist completely absent from this sample.

The dearth of hip and wrist fractures at Wharram Percy validates the statement made by Agarwal and Grynpas (1996), who maintain that osteoporotic fractures, specifically those of the proximal femur, are notably absent in the archaeological record (however see Brickley, [2002]; Dequeker et al., [1997] and Lees et al., [1993] for some exceptions). While this phenomenon can be explained in several ways, [i.e. past individuals died before hip fractures presented, since these breaks normally occur in modern individuals over 70 years of age (Mays, 1996)], these authors go on to state that bone loss in the past does not reflect contemporary patterns of osteopenia. As examples, Agarwal and Grynpas state that the age-related bone loss observed in many archaeological samples is often higher in younger females (see Martin and Armelagos, 1979; 1985 for an example) and is present in males. While the first statement is indeed at odds with what is generally found in clinical populations, the second is not. Medical research is now demonstrating that modern males experience a linear pattern of age-related bone loss, with diminutions occurring in the total body (11%), spine (9%) and

legs (15%) (Gennari and Nutti, 1996). While this loss is certainly not as severe as that which occurs women, it is present and should be acknowledged.

3.3.2. Trabecular bone loss

Due to its rapid turnover rate, hormonally or age-induced bone loss is initially more severe in the trabecular compartments of the skeleton relative to areas formed predominantly of cortical tissue (Brickley and Howell, 1999; Perzigian, 1973; Stini, 1990; 1995; Weinstein et al., 1981). Unlike cortical bone, which is very compact, trabecular tissue is porously fashioned from an inter-connected, three-dimensional lattice-work of thick vertical columns and thinner horizontal struts separated by marrow spaces (Jenson et al., 1990; Kanis, 1996; Keaveny et al., 2001). These columns, struts and spaces are economically orientated in accordance to the compressive and torsional stresses most commonly applied to a particular skeletal element, thereby maximizing that element's mechanical strength and functional integrity while minimizing bulk and weight (Currey, 1990; Kanis, 1996; Keaveny et al., 2001). Unfortunately, this compromise means that even minor losses of trabecular tissue, losses which would minimally alter overall BMD, can result in substantial changes in the strength and integrity of the trabecular network (Brickley and Howell, 1999). Given this, examination of not only the quantitative but also the qualitative characteristics of trabecular bone, specifically measurements of its strength, rigidity and interconnectivity, is vital in understanding bone loss in the past and present (Agarwal and Grynpas, 1996).

Analyses of trabecular bone loss in the past reveals a complexity of patterns (Agarwal, 2001; Kneissel et al., 1994; Kneissel et al., 1997; Lees et al., 1993; McEwan et al., 2004; Poulsen et al., 2000; Velasco-Vázquez et al., 1999; Vogel et al., 1988). In her doctoral research of age and sex related changes in the BMD and trabecular architecture of Roman, Medieval and Post-medieval British archaeological populations, Agarwal (2001) found that: (i) significant sex differences existed only in the Post-medieval sample; (ii) significant decreases in trabecular BMD, structure and connectivity were found only in the Roman and Post-medieval males; and (iii) no significant changes in the preceding histomorphometric parameters were noted between the middle-aged and older females of all three samples. Instead, these women demonstrated relatively greater bone loss in the younger age category and preservation of trabecular BMD and architecture in the peri- and post-menopausal years. Agarwal (2001) suggested that this pattern of trabecular change resulted from the increased parity and extended periods of breastfeeding likely practiced by these women, and noted that although pregnancy and lactation are high bone turnover states which can adversely affect the maternal skeleton, some clinical evidence suggests that repeated pregnancies can augment bone density in healthy females over time (Fox et al., 1993; Sowers, 1996). Additionally, clinical research indicates that for most women complete recovery of lost bone occurs 12-24 months post-partum (Kalkwarf and Specker, 2002; Phillips et al., 2000). That the younger females of these samples exhibited greater bone loss may simply be indicative of women that were immediately post-partum or breastfeeding at the time of death (Agarwal et al., 2004).

Greater rates of peri- and post-menopausal bone loss in contemporary individuals, when compared to those of archaeological samples, have also been found by other investigators (Lees et al., 1993; Poulsen et al., 2000; Vogel et al., 1988). Using dual energy x-ray absorptiometry to measure the BMD of the proximal femur, Lees and colleagues (1993) conclude that rates of bone loss were significantly greater in modern pre- and post-menopausal British women when compared to those found in an 18^{th} –19^{th} century cemetery sample. The authors suggest that an increased level of physical activity may have been but one exogenous factor preserving femoral BMD in the archaeological sample. Similar findings were also noted by Poulsen and colleagues (2000) in their medieval sample of 49 Danish skeletons (AD 1000-1250). Although the younger medieval women of the sample exhibited lower BMD scores when compared to a contemporary Danish group of females, this trend was reversed in the older (> 50 years) age category. To explain the apparent discrepancies in the observed BMD scores of younger versus older and medieval versus modern women, Poulsen and co-workers proffer the hypothesis of selective mortality. They state that the physiological demands associated with high birth rates and prolonged periods of lactation would have led to reduced BMD and increased mortality among those young medieval women of questionable constitution. Thus, from an epidemiological perspective, the increased incidence of osteoporosis among elderly women of contemporary origins may be explained by the survival of a female subpopulation that, through the forces of natural selection, would have died prematurely in earlier centuries.

Whereas the preceding authors found minimal peri- and post-menopausal bone loss in their samples, other researchers observed comparably modern rates of trabecular bone loss in the past. For example, Kneissel and colleagues (1994) found that the trabecular bone of their Bronze age skeletal sample (N=18) followed contemporary age and sex-related patterns of change. As with modern individuals, BMD values decreased significantly between the middle and older aged males and females. Histomorphometric examination of the vertebral body and femur revealed increased perforation and loss of individual trabeculae, resulting in the overall diminution of interconnectivity. These losses were especially apparent in the older females, suggesting hormonally induced changes in the trabecular tissues of these individuals. Paradoxically, the findings of Kneissel and colleagues (1994) were not replicated by Vogel and colleagues (1988) in their examination of a historical (AD 3^{rd} to 7^{th} century) German cemetery sample (N=110). Utilizing identical histomorphometric measurements of trabecular connectivity and volume, Vogel and co-workers found increased interconnectivity of trabeculae in the iliac crest of the sampled women when compared to age-matched modern controls. This finding did not extend to the males of the sample, leading the authors to conclude that the increased reproductivity of these women likely contributed to the preservation of their trabecular architecture.

3.4. CONCLUSIONS

A review of studies evaluating cortical bone loss in the past has revealed three trends. The first trend is one of progressive cortical bone loss after the attainment of peak bone mass and with advancing age (Carlson et al., 1976; Cho, 2002; Mays et al.,

1998; McEwan et al., 2004; Perzigian, 1973). The second trend is one of decreased cortical mass in women, both absolutely and relatively, when compared to that of the sampled men (Carlson et al., 1976; Cho, 2002; Dewey et al., 1969; Martin and Armelagos, 1979; 1985; Rekewant, 1994; Ruff and Hayes, 1983; Ruff et al., 1984; Thompson and Gunness-Hey, 1981; Thompson et al., 1981; Van Gerven et al., 1969), and the third trend, which finds similar patterns of cortical bone loss between past and contemporary populations (Mays, 1996; 2000; Van Gerven et al., 1969).

In contrast, a large majority of studies examining the diminution of trabecular bone found significantly different patterns of loss when modern and archaeological samples were compared. Although bone loss was greater in younger women from archaeological sites located in Britain (Agarwal, 2001; Agarwal et al., 2004), Denmark (Poulsen et al., 2000), and Germany (Vogel et al., 1988), peri- and postmenopausal bone loss was also minimized in these same samples. Temporally diverse patterns of reproductivity and lactation were commonly cited as reasons for these discrepancies (Agarwal, 2001; Agarwal et al., 2004; Poulsen et al., 2000; Vogel et al., 1988).

Table 3.1(a) Studies of cortical bone loss in the archaeological record.

References	Archaeological sample	Methodology	Fracture(s)
Burr et al., 1990	**Origin:** Pecos, New Mexico (14^{th}-19^{th} CAD) **Size:** n=55 (27 ♀ / 28 ♂) **Age range:** 21-60 years	Histological measurements of the femur	None noted
Carlson et al., 1976	**Origin:** Native American population from Missouri (AD 1540-1700) **Size:** n=40 (21♀ / 19 ♂) **Age range:** 20-55+ years	Measurement of cortical thickness, cortical area and diameter of the femur	None noted
Cho, 2002	**Origin:** Imperial Roman necropolis (2^{nd}-3^{rd} C AD) **Size:** n=149/ **Age range:** 20-50 years	Histomorphometric analysis of the rib, femur and iliac crest	Vertebrae
Dewey et al., 1969	**Origin:** 3 Sudanese Nubian populations: Meriotic (350 BC- AD 350); X-group (AD 350-550);Christian (AD 550-1300) **Size:** Meriotic n=46 (29 ♀ / 17 ♂); X-group n=105 (63 ♀ / 42 ♂); Christian n=52 (28 ♀ / 24 ♂) **Age range:** 16- 50+ years	Measurement of cortical thickness on femur	None noted
Drusini et al., 2000	**Origin:** Vicenza, NE Italy (ca AD 730) **Size:** n=66 (33 ♀ / 33 ♂) **Age range:** 20-51+ years	Anthropometric measurements of the femur including cortical thickness, cortical area and medullary area	None noted
Ericksen, 1980	**Origin:** 3 Native American populations: SW Pueblo (AD 1130-early Spanish period); Arikara of S Dakota (AD 1675-1845); Alaskan Eskimo (late 18^{th} – 20^{th}C) **Size:** Pueblo n=90 (45 ♀ / 45 ♂); Arikara n=102 (34 ♀ / 68 ♂); Eskimos n=75 (38 ♀ / 37 ♂) (*note samples size are based on information provided in table 1, p 244). **Age range:** 18-50+ years	Histological analysis of the cortical bone of the femur	None noted

Table 3.1(b). Studies of cortical bone loss in the archaeological record (continued)

References	Archaeological sample	Methodology	Fracture(s)
Ericksen, 1976	**Origin:** 3 Native American populations: SW Pueblo (AD 1130-early Spanish period); Arikara of S Dakota (AD 1675-1845); Alaskan Eskimo (late 18th – 20thC) **Size:** Pueblo n = 142; Arikara n=134; Eskimos n=123; both ♀+♂ represented **Age range**: 18-50+ years	Radiographic measurements of femur + humerus; histologic indices of cortical thickness	None noted
Gunness-Hey, 1987	**Origin:** Kodiak Island Alaska 500 BC-AD 1700) **Size:** N=90 (39 ♀ / 51 ♂) **Age range:** 20-40+ years	Photon absorptiometry and histomorphometry of the femoral mid-shaft	None noted
Martin and Armelagos, 1985	**Origin:** 3 Sudanese Nubian samples (Wadi Halfa): Meroitic (0 BC-AD 350); X-group (AD 350-550); Christian (AD 500-1300) **Size:** n=185 (101 ♀ / 84 ♂) **Age range:** 18-50+ years	Microradiographic and histological analysis of the femur	None noted
Martin & Armelagos, 1979	**Origin**: Wadi Halfa, Sudanese Nubia: X-group (AD 350-550) **Size:** n=74 (40 ♀ / 34 ♂) **Age range**: 20-50+ years	Microradiographic and histomorphometric analysis of cortices of the femur	None noted
Mays, 2000	**Origin**: Spitalfields, London, England (1732-1849 AD) **Size**: n=95 (♀) **Age range**: 17-94 years	Radiogrammetry of second metacarpal	Rib, ulna, scapula, fibula
Mays, 1996	**Origin**: Wharram Percy, Yorkshire, England (10th to 16th C AD) **Size**: n=138 (65 ♀ / 73 ♂) **Age range**: 18-50+ years	Radiogrammetry of second metacarpal	Rib and vertebrae
Pfeiffer & King, 1983	**Origin**: 2 Iroquoian ossuary sites: Kleinberg (~AD 1600); Uxbridge (AD 1490 +/- 80) **Size:** Kleinberg n=561; Uxbridge n=457; approximately equal representation of ♀ and ♂ **Age range**: primarily young adults	Radiographs (lumbar vertebrae) and cross-sectional measurements (femurs and second metacarpals)	None noted

Table 3.1(c). Studies of cortical bone loss in the archaeological record (continued)

References	Archaeological sample	Methodology	Fracture(s)
Rewekant, 1994	**Origin**: medieval rural populations, Poland **Size**: n=289 (134 ♀ / 155 ♂) **Age range**: 15-70 years	Radiography and caliper measurements of second metacarpal	None noted
Ruff and Hayes, 1983	**Origin**: Pecos Pueblo, New Mexico (AD 1300-1650) **Size**: n=119 (approx. equal number of ♀ and ♂) **Age range**: 20-50+ years	Measurement of cross-sectional geometric properties of the femur and tibia	None noted
Ruff et al., 1984	**Origin**: 2 Native American populations from the Georgia Coast: pre-agricultural (2200 BC- AD 1150); agricultural (AD 1150-1550) **Size:** pre-agricultural n=20 (12 ♀ / 8 ♂); agricultural n= 20 (9 ♀ / 11 ♂) **Mean age at death**: pre-agricultural 25 years; agricultural 28 years	Measurement of cross-sectional geometric properties of the femur	None noted
Thompson and Gunness-Hey, 1981	**Origin:** 4 Yupiaq-Inupiaq Eskimo populations: St. Lawrence Island, Baffin Island and South Hampton Island (all 19th C); Kodiak Island (700 BC-AD 1700) **Size:** St. Lawrence Island n=53 (32♀ / 21 ♂); Kodiak Island n=92 (39 ♀ / 53 ♂); Baffin Island n=44 (20 ♀ / 24 ♂); South Hampton Island n=69 (39 ♀ / 30 ♂) **Age range:** 15-50+ years	Histomorphometric analysis of femoral cortical indices	Distal femur
Thompson et al., 1981	**Origin:** Inupiaq Eskimos, Baffin Island **Size:** n=44 (20 ♀ / 24 ♂) **Age range:** 18-55+ years	Photon absorptiometry and bone core analysis of the femur.	None noted
Van Gerven et al., 1969	**Origin**: prehistoric Mississippian population (Missouri) (AD 1540-1700) **Size**: n=43 (23 ♀ / 20 ♂) **Age range**: 22-65 years	Roentgenographic and direct measurement of the cortical thickness of the femur	None noted

Table 3.2(a). Studies of trabecular bone loss in the archaeological record

References	Archaeological sample	Methodology	Fracture(s)
Agarwal, 2000	**Origin**: 3 British skeletal populations: Roman (Eastern Cemetery, London Borough of Tower Hamlets [2nd-4th CAD] and Spitalfields, London [2nd CAD]); Medieval (Wharram Percy, Yorkshire [10th -16th CAD]); Post-medieval (Farringdon Street Cemetery, London [1770-1849 CAD]) **Size**: Eastern Cemetery: (11 ♀ / 18 ♂); Roman Spitalfields: (4 ♀ / 6 ♂); Wharram Percy: (33 ♀ / 32 ♂); Farringdon Street: (26 ♀ / 41 ♂) **Age range**: 17-50+ years	DXA[1] and histomorphometric analysis of the 4th lumbar vertebrae	None noted
Agarwal et al., 2004	**Origin:** Wharram Percy, Yorkshire, England (10th-16th CAD) **Size:** n=54 (30 ♀ / 24 ♂) **Age range:** 18-50+ years	Histomorphometric analysis of the 4th lumbar vertebrae	None noted
Brickley and Howell, 1999	**Origin**: 2 cemetery sites from London, England: St. Bride's Lower Churchyard and Cross Bones Burial Ground (AD 1700-1850) **Size**: n=79 (35 ♀ / 38 ♂ / 6 unsexed) **Age range**: 15-55+ years	Close range photo-grammetry of the fourth lumbar vertebrae	None noted
Kneissel et al., 1997	**Origin:** Sayala, Nubia (6th-10th CAD) **Size:** n=65 **Age range:** 0-60 years	Scanning electron microscopy, stereo-photography and histomorphometry of the fourth lumbar vertebra	None noted

[1] **dual energy x-ray absorptiometry**

Table 3.2(b). Studies of trabecular bone loss in the archaeological record (continued)

References	Archaeological sample	Methodology	Fracture(s)
Kneissel et al., 1994	**Origin**: Franzhausen I necropolis, Austria (4000y BP) **Size**: n=18 (9 ♀ / 9 ♂) **Age range**: 20-60 years	3-D stereoscopy, DXA[1], radiography, back scattered microscopy, light microscopy and histomorphometry of the fourth lumbar vertebrae and femoral neck	None noted
Lees et al., 1993	**Origin**: Spitalfields, London (AD 1729-1852) **Size**: n=117 (87 ♀ / 30 ♂) **Age range:** 15-89 years (♀) / 25-88 years (♂)	DXA of the proximal femur (femoral neck and Ward's triangle)	Femur
Poulsen et al., 2001	**Origin**: medieval Christian cemetery, Norby, Denmark (AD 1000-1250) **Size**: n=49 (20 ♀ / 29 ♂) **Age range:** 26-72 years (♀) / 29-80 years (♂)	DXA measurement of the femoral neck	None noted
Sambrook et al., 1988	**Origin:** Late Roman Pella, Jordan (AD 320-340) **Size:** n=1 (♂) (case study) **Age range:** 50-60 years old	Radiography and DPA[2]	Vertebra
Velasco-Vázquez et al., 1999	**Origin:** Gran Canaria, Canary Islands (2080 +/- 60 bp-700+/- 50 bp) **Size:** n=273 (97 ♀ / 166 ♂ / 10 unsexed) **Age range:** very young (symphyseal stage I)-mature (symphyseal stage III – Suchey-Brooks method)	Histomorphometry of the proximal tibia	Note high prevalence of osteoporosis, but no fractures noted
Vogel et al., 1988	**Origin:** Western Germany (3^{rd}-7^{th} CAD or 13^{th}-15^{th} CAD) **Size:** n=110 (37 ♀ / 73 ♂) **Age range:** 7-67 years	Quantitative histomorphometric analysis of the iliac crest	None noted

[1] dual energy x-ray absorptiometry
[2] dual photon absorptiometry

Table 3.3. Studies of both cortical and trabecular bone loss in the archaeological record

References	Archaeological sample	Methodology	Fracture(s)
Dequeker et al., 1997	**Origin**: Lisht, Upper Egypt (1990-1786 BC) **Size**: n = 1 (♀) (case study) **Age range**: > 50 years	Radiographic measurements of long bones and claviculae	Femoral neck and vertebrae
Ekenman et al., 1995	**Origin:** Stockholm, Sweden (AD 1300-1530) **Size:** n=343 (156 ♀ / 187 ♂) **Age range:** 20-59 years	Radiography of the radius, second metacarpal and femur; photon absorptiometry of the humerus, femur and tibia; single energy scanning of the radius	None noted
Foldes et al., 1995	**Origin**: Nessana, Negev Dessert, Israel (6th C AD) **Size**: n=1 (♀) **Age range**: 35-40 years	SPA (radius)[1] DXA (spine, femur)[2] Histomorphometry (ilium)	Vertebrae and ribs
Mays et al., 1998	**Origin**: Wharram Percy, Yorkshire, England (10th to 16th C AD) **Size**: n=144 (62 ♀ / 82 ♂) **Age range**: 18-50+ years	DXA (femur) Radiogrammetry (femur)	Rib and vertebrae
McEwan et al., 2004	**Origin:** Wharram Percy, Yorkshire, England (10th-16th CAD) **Size:** n=101 (43 ♀ / 58 ♂) **Age range:** 19-50+ years	DXA (radius) Radiogrammetry	Rib and vertebrae
Perzigian, 1973	**Origin**: 2 Native American populations: Indian Knoll (2500-2000 BC); Pete Klunk (50 BC – AD 250) **Size:** n=271 (101 ♀ / 170 ♂) **Age range**: 20-50+ years	Photon absorptiometry (radius – midshaft and distal end)	None noted
Weinstein et al., 1981	**Origin:** Chancay, Peru (AD 400-1600) Size: n=1 (♂) (case study) Age range: 46 +/- 4 years of age	Histomorphometry of transileal bone cores	None noted

[1] **single photon absorptiometry**
[2] **dual energy x-ray absorptiometry**

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CHAPTER FOUR: MATERIALS AND METHODS

4.1. INTRODUCTION: THE OBJECTIVES

The objectives of this research are: (i) to examine the relationship between age, trabecular bone quality of the iliac crest, and cortical and trabecular bone quantity of the radius in a Medieval British skeletal sample; and (ii) to determine the methodological feasibility of utilizing trans-iliac bone cores in the histomorphometric examination of archaeological skeletal material. To achieve these objectives, a skeletal sample consisting of twenty-three females from the medieval peasant population of Wharram Percy (Yorkshire, England) was selected for examination. Aspects of the Wharram Percy collection which render it suitable for the purposes of this research include: (i) excellent preservation of skeletal remains, (ii) a large number of older adults ($\geq$ 50 years), thereby facilitating the study of age-associated bone loss and fracture, (iii) the availability of archaeological and historical data regarding the lifestyle of these medieval inhabitants, and (iv) the use of this collection in previous studies on bone loss (Agarwal, 2001; Agarwal et al., 2004; Mays, 1996; Mays et al., 1998; McEwan et al., 2004).

4.2. HISTORICAL BACKGROUND: THE PEOPLE OF WHARRAM PERCY

The medieval habitation site of Wharram Percy is located on the northwestern scarp of the chalk wolds in Yorkshire, England (Fig. 4.1). Elevation of the area is approximately 150 meters above sea level, with the plateau dissected by a number of deep and narrow valleys. Springs emerging from the chalk and underlying levels of Jurassic clay would have provided a constant source of fresh water for past inhabitants, likely making this area a preferred site of human activity and settlement (Hurst, 1984). Archaeology supports this likelihood, with lithic finds and land clearances and earthworks demonstrating the presence of Mesolithic hunters and Neolithic farmers respectively (Atkins and Tompkins, 1986). The earliest indication of human settlement dates to the Iron Age (circa 500 BC); additional archaeological evidence of Roman (circa AD 150) and eighth century Anglo-Saxon occupations have also been recovered (Atkins and Tompkins, 1986).

The first documentary evidence of Wharram Percy is provided by the Domesday Book, a national survey conducted in AD 1086 by King William the Conqueror for the purpose of levying taxes (Ashley, 2002; Hurst, 1984). At this time, the area belonged to the king and was divided between two manor houses (Hurst, 1984). Further documentation indicates that ownership of Wharram Percy in the mid twelfth century was divided between two families, the Percies and the Chamberlains (Hurst, 1984). The village remained under dual ownership until AD 1254, when it was purchased outright by Peter de Percy and the two manor houses were consolidated into one (Atkins and Tompkins, 1986; Beresford and Hurst, 1990). During the fourteenth century, Wharram Percy reached its zenith – with approximately thirty households and a population of 150 individuals (Atkins and Tompkins, 1986). The Percies maintained ownership of the

village until 1403, when it was then exchanged with another family, the Hiltons, for land in Northumberland (Hurst, 1984). Depopulation of the medieval village began in earnest around this time, likely owing to the enclosure of agricultural land by the Hiltons for the purpose of sheep grazing (Hurst, 1984; Muir, 1982). With the means of their livelihood destroyed, the peasant population of Wharram Percy migrated from the area, leaving the medieval village site deserted by AD 1500 (Hurst, 1984). However, the surrounding parish communities of Raisthorpe, Thixendale, Burdale and Towthorpe continued to use the village church, St. Martin's, for another four hundred years (English Heritage, 2003), and attendance at the Wharram Percy parish dropped sharply only after the construction of a new church in Thixendale in AD 1870 (English Heritage, 2003).

Life of the rural medieval peasant was frequently arduous. Diet was habitually restricted to a small selection of food items and was often lacking in calories and essential nutrients, specifically protein, calcium and vitamins A, C and D (Gies and Gies, 2002). The peasant population of Wharram Percy likely subsisted on beef, mutton, snails, and a bread made from wheat and barley (Atkins and Tompkins, 1986). Bones of cod and haddock were found in 13^{th}-15^{th} century deposits, suggesting that inhabitants may have supplemented their diet with marine resources during this period (Atkins and Tompkins, 1986). However, isotopic analysis of skeletal remains from this site indicate minimal contribution of marine or C_4 based foods to the average diet (Richards et al., 2002). Instead, $\delta^{15}N$ values are indicative of mixed food consumption, with a large protein contribution from both animal (meat and dairy) and plant sources (Richards et al., 2002). This diet remained relatively uniform over time, with no detectable differences between adult males and females (Richards et al., 2002).

The workload of the medieval peasant was gender specific, with men tending to laborious activities that removed them from the domestic area of the croft, specifically the plowing of fields, felling of trees, carting of goods and herding of animals (Bennett, 1987). Although women did work in the fields as planters, weeders, reapers and gleaners during harvest time and could be employed to perform "male" tasks during periods of acute labor shortage, their daily life emphasized chores within the domestic sphere, i.e. gardening, dairying, weaving and tending livestock, combined with the countless other duties involved in the rearing of children and the running of a household (Bennett, 1987; Goldberg, 1992; Mays, 1996). At Wharram Percy, however, the gender-specific division of labor that prevailed throughout this time period may have been more fluid. In an examination of activity-related osseous change in the spine of 59 individuals, Derevenski (2000) found that, although women were less affected than men, the distribution and patterning of change was very similar between the sexes. These results suggest that both the men and women of Wharram Percy were subject to similar forms and levels of spinal stress.

Although it is commonly assumed that medieval couples wedded early and that married peasant women were perpetually pregnant or nursing (Bennett, 1987), some historical documents suggest otherwise. While subject to both regional and temporal variations, poll tax papers indicate that many medieval peasants did not wed at all and those that did practiced a distinctively northwest European marriage regime characterized by late companionate unions and the formation of small nuclear

households (Bennett, 1987; Goldberg, 1992; Grauer, 1991). For those peasant women that did marry, many could have experienced negligible reproductive success due to the bodily effects of poor nutrition and health combined with heavy workloads (Bennett, 1987; Roberts and Cox, 2003), which can contribute to amenorrheic episodes thereby compromising a woman's ability to conceive. For those that did become pregnant, extended periods of lactation may have also limited their reproductive rates (Bennett, 1987; Gies and Gies, 2002). For example, through the examination of carbon and nitrogen stable isotopes in bones and teeth, Richards and colleagues (2002) suggest that the weaning of children at Wharram Percy occurred around two years of age. Additional research examining calcium and strontium levels in the infant remains of this skeletal population also indicate a maximal weaning age of two years (Mays, 2003). Allowing for the cessation of lactation and the recommencement of menstruation, it is possible that the uncontrolled birth interval extended some 2.5 years (Bennett, 1987).

Although the health and psychological benefits of extended lactation for both mother and child were recognized during medieval times (Fildes, 1995), childhood survival was still tenuous at best. For those pregnancies that went to term, the high rate of mortality ensured that 12-20% of children died during infancy and an additional 12-20% perished prior to reaching sexual maturity (Bennett, 1987). Factors such as accidents, epidemics, gastro-intestinal infections, poor nutrition and poverty would have each contributed to these percentages (Orme, 2001; Mays, 1998). At Wharram Percy, the skeletal remains of children suggest that these individuals endured substandard nutrition and greater disease loads when compared to those offspring of the urban poor living during the Industrial Revolution (Mays, 1998). Marked deficiencies in cortical bone thickness and index relative to recent subjects (Mays, 1999) and a high prevalence of sinusitis, acute trauma, respiratory infections and rickets (Lewis, 2002) suggest that these children were highly susceptible to surrounding environmental stresses.

In terms of adult longevity, the paleodemographic research conducted by Grauer (1991) on the medieval inhabitants of York, an urban center lying some 20 miles from Wharram Percy, suggest that female mortality peaked during the age interval of 25-35 years. In contrast, male mortality climaxed between 35-45 years of age. At Wharram Percy, the archaeological data suggest that once the inhabitants attained adulthood, they had a 40% chance of surviving to at least 50 years of age (Mays, 1998).

4.3. MATERIALS AND ASSOCIATED LIMITATIONS

4.3.1. Materials

All individuals chosen for the purpose of examination originate from the medieval peasant population of Wharram Percy (10^{th} –16^{th} centuries AD). This large skeletal collection is housed at Fort Cumberland, Portsmouth, England and is curated by Dr. Simon Mays of English Heritage. Each chosen individual is female, of European ancestry, and falls into one of the following three predetermined age categories: young adult (18-29 years), mid adult (30-49 years), or older adult (50+ years) (Mays, 1996). Thirty-one females were initially selected and categorized into the appropriate subsamples (Table 4.1a). Due to the inherent fragility of some of the skeletal remains,

however, only twenty-three individuals were successfully sampled and subsequently measured for analysis. The age distribution of these women is outlined in Table 4.1b.

4.3.2. Limitations

Regardless of their origin, all skeletal samples are subject to limitations or biases. These biases must be identified prior to analysis in order to minimize their effects on the final interpretations of the data (Rogers, 1999). In regards to the Wharram Percy skeletal collection, several biases must be acknowledged. The first of these is the preservation of the skeletal sample.

Skeletal preservation in this particular collection is considered to be very good due to the alkaline nature of the soil (pH values 7.3-8.0) (Mays, 1998). Gross inspection of the remains reveals negligible erosion of external bony surfaces, suggesting minimal contamination by the surrounding burial matrix (Mays, 1998). However, the processes of diagenesis are such that significant modifications to the quantity and quality of bone may occur even though the outer surfaces appear relatively unscathed (Mays et al., 1998). To address this potential problem, Mays and colleagues (1998) examined the femoral bone mineral density (BMD) of 144 individuals from Wharram Percy. Using dual energy x-ray absorptiometry (DXA), BMD scores were compared to similar results generated from medieval and contemporary reference populations. The findings of this research indicate that the effects of diagenesis on BMD measurements are minimal. In a separate study, however, the analysis of thin sections with scanning electron microscopy have revealed extensive microbiological deterioration of histological structures within the bone (Mays et al., 2001). While this deterioration will prove to be problematic for the examination of bone remodeling parameters, previous studies conducted on this skeletal collection suggest that the microarchitectural analysis of trabecular bone is still viable (Agarwal, 2001; Agarwal et al., 2004). Given the methodology of the present study, this viability proves to be very positive. Nevertheless, it must be remembered that the intrinsic characteristics of osteopenic/ osteoporotic bone, specifically the decreased BMD and diminished microarchitectural integrity of the tissue, may lead to accelerated post-burial disintegration of affected remains (Walker, 1995). The recovery of inherently fragile perinatal skeletons (n=66) from the Wharram Percy site does suggest, however, an increased likelihood that remains of osteopenic/osteoporotic individuals would also survive this post-burial environment (Mays, 1998).

The second bias associated with this collection is the cross-sectional nature of the sample. As stated by Mays (1998), this skeletal assemblage represents an aggregate of individuals accumulated over a very long period of time. Although it is assumed that the socio-economic status of these individuals remained relatively constant, variations in climate and health over time would have differentially affected the compilation of this skeletal sample. As a result, the overall longevity inferred from the skeletal sample may not be representative of individual longevity in any given period of time. This problem may be exacerbated by the nonstationary nature of this sample. Emigration of both males and females from rural communities to nearby urban centers was commonplace throughout the medieval period (Goldberg, 1992). At Wharram Percy, adult sex ratios (1.58:1) suggest that a female-led migration, likely to the nearby urban

centers of York or Hull, was probable (Fig. 4.1.) (Mays, 1998). This, in turn, could affect any mean age-at-death estimations and distributions (Jackes, 1993; Johansen and Horowitz, 1986; Milner et al., 2000). Mays (1998) states, however, that the sex ratios in all three adult groups at Wharram Percy do not statistically differ from one another, thus the impact of emigration on sample age-at-death distributions is likely to be small.

The third source of bias associated with this collection is the need to estimate age-at-death. In this sample, the age-at-death estimates were previously assessed by Mays (1996) on the basis of dental attrition. Wear on the molar teeth was recorded using a modification of Brothwell's (1981) system and calibrated by a methodology analogous to that of Miles (1963). Unlike other methods, the dental estimation of age-at-death can be advantageous in that it does not rely upon chronological standards developed from modern reference populations. As stated by Mays (1998), age-associated morphological changes in the human skeleton are influenced by a multitude of intrinsic and extrinsic factors, thereby making the aging process highly variable for each individual. Given this, chronological standards developed on modern populations - specifically on individuals who are likely intrinsically and extrinsically different from past peoples - may not be applicable to archaeological samples. The use of dental wear to estimate age negates this problem because (i) factors contributing to dental wear, specifically the structure of the tooth, the mechanics of mastication and the effects of dietary constituents on teeth, are understood; and (ii) chronological standards of dental wear are developed within the study sample through the examination of attrition rates found in immature individuals. Unfortunately, this latter point assumes (i) that there is a sufficient number of immature individuals ($n>20$) from which internal standards of dental wear can be calibrated and (ii) that all individuals within a given sample experienced similar rates of wear - an assumption which becomes increasingly problematic given the cross-sectional nature of most archaeological samples. Fortunately, the Wharram Percy collection does have sufficient numbers of immature individuals from which adult wear estimates can be calibrated (Mays, 1998). Furthermore, a study conducted by Brothwell (1981) suggests that rates of dental attrition in British children remained relatively constant from the Neolithic period to medieval times. Given this stability, it is unlikely that great differences in the rates of dental wear would be notable in individuals existing within the same community and subsisting on similar types of food (Mays, 1998).

An additional problem associated with dental wear estimates of age-at-death is tooth loss. The loss of teeth in archaeological skeletal samples is commonplace. Aside from problems associated with the excavation and recovery of dental remains; several dental diseases, specifically caries and periodontal inflammation, can lead to ante-mortem tooth loss (Costa, 1982; Hillson, 2001; Mays, 1998). Heavy wear can also precipitate loss through the continuous eruption of teeth to maintain occlusion (Clarke and Hirsch, 1991). Teeth that are lost prior to death are not only removed from the study sample, but their absence may also minimize the amount of wear sustained by their occlusal partner (Mays, 1998). Given this, it is reasonable to expect that non-occluding teeth would underestimate the chronological age of the individual. However, a study conducted by Mays (2002) on a 19th century Dutch cemetery sample suggests that ante-mortem tooth loss has no demonstrable effect on the progression of dental wear.

Unfortunately, the attrition rates in the selected study group are considered to be slow (Constandse-Westermann, 1997); thus personal idiosyncrasies, such as abrasion and non-masticatory uses of the dentition, would have played a greater role in the variation of wear patterns and rates between individuals (Mays, 2002). This, in turn, would minimize the accuracy with which age-at –death can be estimated. Fortunately, the rates of attrition exhibited by the individuals at Wharram Percy are sufficiently marked to allow reliable measurements of dental wear (Mays, 1998). Given this, the age estimates assessed by Mays (1996) were used in this analysis.

The fourth and final bias associated with this collection is the need to determine the sex of each individual. Sex determination within a paleodemographic context is dependent upon (i) the magnitude of sexual dimorphism between males and females within a population and (ii) the amount of within-sex variation (Meindl and Russell, 1998). Thus the determination of sex is very group specific and requires the selection of an appropriate reference population to minimize inaccuracy and bias (Meindl and Russell, 1998). Standard osteological indicators used to determine the sex of individuals include the dimorphic characteristics of the skull and pelvis, with increased reliability placed on the latter (Buikstra and Ubelaker, 1994). The sexing of all adult individuals from Wharram Percy had been previously been performed by Mays (1996) using these osteological indicators. No discrepancies with the original assessments of sex were noted by this author, thus the original determinations were used in this analysis.

4.4. METHODS AND ASSOCIATED LIMITATIONS

4.4.1. Measurement of trabecular bone quality and associated limitations

Measurements of trabecular bone quality were generated from the histomorphometric analysis of trans-iliac bone cores. This method was chosen for three reasons. First, current clinical study uses trans-iliac bone cores, or biopsies, as a preferred method for the structural assessment of osteoporosis and other metabolic bone diseases (Parfitt, 1992; Rao, 1983). By employing the same experimental protocol, this research provides paleopathological data that is methodologically comparable to bone quality data generated from modern day individuals. Second, the trans-iliac bone core, when compared to other methods of histomorphometric sampling, minimizes the tissue destruction of non-reproducible archaeological skeletal material and provides specimens with nominal architectural distortion thereby facilitating structural analysis (Foldes et al., 1995; Rao, 1983). Finally, if proven to be a reliable method for the structural assessment of trabecular bone in archaeological skeletal material, trans-iliac bone cores would provide yet another methodological option for bioarchaeologists interested in the examination of bone loss in past populations.

Despite these advantages, however, the use of the trans-iliac bone cores as a means of evaluating trabecular quality is not only destructive, but also requires substantial sample preparation (Müller et al., 1998). Additionally, the histomorphometric analysis of trans-iliac thin sections provides two dimensional data on a three dimensional structure, thereby necessitating the use of some derived indices to measure the architectural parameters of the specimen (Hildebrand et al., 1999; Parfitt

et al., 1983). Finally, the structural indices of bone quality may vary between skeletal sites, specifically between those weight bearing and non-weight bearing bones (Parfitt et al., 1983). Researchers have found, however, significant correlations between the structural indices and mechanical properties of trabecular bone in both the weight-bearing vertebral body, an area which is particularly prone to osteoporotic fracture in clinical populations, and the non-weight bearing iliac crest (Klein and Gunness, 1992; Parfitt, 1992; Thomsen et al., 1998).

4.4.1.1. Collecting the trans-iliac bone cores

A five centimeter isolateral inverted triangle was outlined on each innominate bone with the anterior superior iliac spine serving as a guide and the iliac crest border forming the base of the triangle (Fig. 4.2) (Rao, 1983). Bone cores measuring ten millimeters in diameter were then drilled from the center of this triangle using a diamond tipped plug-cutter inserted into a battery operated hand drill mounted on a portable drill press. With the exception of two individuals, who had cores drilled from both ilia for control purposes, each woman had one bone sample removed from either the right or left innominate. Factors which dictated which innominate was used included the presence and condition of the area to be sampled. Since no differences in bone mass or remodeling between the right and left iliac crest have been reported (Klein and Gunness, 1992), it was assumed that either side could be used for experimentation. Only those specimens that remained intact (i.e. had cortex on both sides of the core) were prepared and used in the ensuing analysis. All trans-iliac bone specimens were collected at Fort Cumberland, Portsmouth, England. Samples were then packaged and transported to laboratory facilities located at the University of Alberta, Edmonton, Canada where subsequent methodological procedures and analyses were conducted.

4.4.1.2. Embedding, sectioning and photographing of the trans-iliac bone cores

All specimens were cleaned in a solution of 70% ethanol and 30% distilled water. This method allows quick drying of osseous tissue and prevents excessive damage to the bone (Agarwal, 2001). Once dry, specimens were placed cortical side up in labeled plastic casting moulds and embedded in an epoxy resin (#105) and hardener (#205) manufactured by West System®. This particular embedding medium was chosen because: (i) it has a mixing time of one minute and a pot life of nine to twelve minutes allowing sufficient time to properly embed the specimens, (ii) it was sufficiently durable to allow the thin sectioning of the bone, (iii) it dried to a pale yellow finish making it easy to photograph the specimens, and (iv) it was relatively inexpensive (West System User and Product Guide). The only caveat associated with the use of this product was that casting layers could be no thicker than ½ an inch due to the excessive buildup of exothermic heat leading to imperfect permeation of the specimen and melting of the plastic mould. Once the moulds were filled to the appropriate levels, each specimen was then vacuum impregnated for two to three minutes. Specimens were then removed from the vacuum and left to cure for 24 hours.

All thin sectioning was performed on an Isomet 11-1180 low speed saw, manufactured by Buehler, Ltd. Specimens were mounted in a chuck and a thick section to the approximate center of the core was taken using a diamond wafering blade. This was done to (i) provide a flat working surface for subsequent thin sections, (ii) to maximize the amount of trabecular bone included in each specimen and (iii) to minimize the amount of peripheral damage caused by the drilling. Using the Isomet micrometer to ensure consistency in specimen thickness, three to five consecutive thin sections of 200-250 micrometers (μm) were then removed from the embedding block parallel to the long axis of the core in accordance with the method utilized by Chappard and colleagues (1999). Although these sections are thicker than those found in some clinical studies (Chappard et al., 1999; Thomsen et al., 1998), Roberts and Wakely (1992) suggest that thick slices are preferable for trabecular bone due to the greater volume of material available for analysis. Once thin sectioning was complete, specimens were cleaned in distilled water, allowed to dry and then mounted on slides using Permount. Specimens were then digitally photographed at 7.5x magnification with a Nikon Coolpix 995 digital camera mounted on a WILD M5 macroscope.

4.4.1.3. Image analysis of trans-iliac bone cores

The histomorphometric investigation of thin sections was performed using the image analysis program SigmaScan Pro 5.0. Digital images of the thin sections were first imported into SigmaScan. Prior to measurement, distance and area were calibrated using a "2-point" image calibration tool provided by the program. This tool converts the old distance and area measurements (pixels) into new, pre-defined measurement units (millimeters and millimeters squared). The calibration of each image pixel was derived from the digital photograph of a micrometry slide taken at 7.5x magnification. Once distance and area were calibrated, the trabecular architecture captured in each image was measured twice using the tracing tool provided by the program to select the desired area of interest. The two measurements were then averaged and used to calculate the following four structural parameters for each specimen (Chappard et al., 1999; Parfitt et al., 1987):

(i) Trabecular bone volume (BV/TV) (%) = trabecular bone area (no marrow spaces) x 100 / total trabecular bone area (including marrow spaces).Trabecular bone area was determined by measuring total trabecular bone area including marrow spaces minus the combined area measurement of all marrow spaces within the region measured.

(ii) Average trabecular thickness (Tb.Th) (μm) = trabecular bone area / ½ perimeter of total area measured. To calculate the perimeter measurement, the demarcation between cortical and trabecular bone was made in accordance to a rule previously defined by Duncan (1973), which states that marrow spaces will be included within the perimeter measurement when the thickness of the trabeculae separating said space from the bone marrow cavity is equal to or less than half the radius of the space under question. The tracing tool was used to outline the marrow-bone interface,

ensuring that the endosteal border of the cortex was not included in the perimeter measurement (Parfitt et al., 1983).

(iii) Trabecular number (Tb.N) (mm^2) = (BV/TV) / Tb.Th. Although commonly interpreted to mean the number of trabeculae, this derived measurement reflects the probability for a test line to cross a trabecular profile on the section.

(iv) Trabecular separation (Tb.Sp) (μm) = 1000 / Tb.N - Tb.Th. This derived measurement calculates the distance across marrow cavities.

These four measurements were selected because they are important architectural parameters and form the basis of any structural analysis of trabecular bone (Hahn et al., 1992; Jinnal et al., 2002; Parfitt et al., 1987). The derived indices were measured in accordance to the parallel plate model, which assumes that the anisotropic orientation of iliac bone forms thick vertical or curved plates connected by pillars (Dempster, 2000; Parfitt et al., 1983). All calculations and nomenclature are in compliance with the ASBMR Histomorphometric Nomenclature Committee (Parfitt et al., 1987).

4.4.2. Measurement of bone quantity and associated limitations

For the purposes of this research the term bone quality refers to the histomorphometric measurement of trabecular bone volume, thickness, number and separation in the iliac crest. In contrast, the term bone quantity denotes the assessment of BMD in both the cortical and trabecular compartments of the radius. All bone quantity measurements employed in this study were previously collected by McEwan and colleagues (2004) using a QDR 4500A dual energy x-ray absorptiometry (DXA) machine to quantitatively assess the one-third, mid and ultra-distal sites of the radius (n=101). The positioning of these sites, all of which are commonly employed in the assessment of radial BMD (Bonnick, 2004), were automatically selected by the DXA machine on the basis of forearm length (McEwan et al., 2004). As stated by McEwan and colleagues (2004), the one-third site is centered at the distance equal to 33% of forearm length, whereas the ultra-distal site is positioned 15 mm proximal to the end plate of the radius. The mid site is that region of interest which falls between the one-third and ultra-distal sites.

DXA is an x-ray technique which generates dual energy photon beams that attenuate both soft tissue and bone (Hays, 2000). By employing mathematical formulae the attenuation within the bone is expressed either as bone mineral content (BMC) (grams) or bone mineral density (BMD) ($grams/cm^2$) (Hays, 2000). To coincide with current clinical guidelines outlined by the World Health Organization, the results of a DXA scan are recorded as T-score values (Hays, 2000; Reginster, 1996). These values, expressed as standard deviations, compare the scanned bone mass scores to the young normal mean with large negative values (i.e. T-scores > -2.5) indicating osteoporotic conditions (Black et al., 2002; Hays, 2000).

Although DXA is a widely accepted non-invasive technique boasting high resolution, great speed and both accurate and reproducible results (Adachi et al., 2000;

Black et al., 2002), there are several limitations associated with its use in clinical and paleopathological contexts. First, measurements of BMC and BMD can vary dramatically not only between individuals but also intra-individually depending upon the age of the person and the skeletal site observed (Miller, 2000; Kanis et al., 2000). Site variance may also contribute to systematic inaccuracies with DXA, particularly in the spinal area (Kanis et al., 1999; Reeve, 1996). Second, certain pathological conditions may impede the accurate measurement of bone density (Kanis et al., 1999). For example, osteoarthritis of the spine can inappropriately elevate the DXA quantification of BMD by increasing the amount of bone via osteophyte development (Colman et al., 1999). Although forearm sites are relatively free of those effects that can confound spinal BMD measurements, the presence of a previous fracture can affect the quantification of both BMC and BMD at those site(s) located close to the afflicted area (Bonnick, 2004). Third, diagenesis may minimize the efficacy of DXA in the paleopathological evaluation of bone loss (Kneissel et al., 1994; Mays, 1996; Stout, 1978; Weaver, 1998). Fortunately, diagenetic effects on BMD measurements were found to be negligible in the Wharram Percy skeletal sample (Mays et al., 1998). Fourth, DXA is a quantification technique designed for living individuals. Since archaeological skeletal specimens lack the soft tissue components of the living, densitometric measurements can be compromised (Mays, 1996). However, this problem was found to be alleviated with the use of rice as a soft tissue substitute (McEwan et al., 2004). Finally, recent research indicates considerable overlap between BMD measurements of populations with and without fractures, implying that the relationship between bone quantity and fracture risk is not linear (Aaron et al., 2000; Audran et al., 2001; Cerroni et al., 2000; Hahn et al., 1992; Schintzler, 1993; Thomsen et al., 1998). Thus, despite the effectiveness of DXA in the determination BMC and BMD, a complete picture of bone health and fracture risk may not be provided by the quantitative assessment of the skeleton.

4.4.3. Statistical analysis

All statistical analyses were conducted using Microsoft Excel 2000. Descriptive statistics, including sample mean, range, standard deviation, and standard error of the mean, were collected for each bone quality parameter measured. Correlations between age, BV/TV, Tb.Th, Tb.N and Tb.Sp, as well as those between the individual measurements of bone quality were examined. Additional correlations between each measurement of bone quality and quantifications of radial BMD at the one-third, mid, and ultra-distal sites were also calculated.

A one-way student's t-test was employed to determine statistical significance between (i) age and BV/TV, Tb.Th, Tb.N and Tb.Sp and (ii) each individual bone quality measurement. Statistical significance was observed when the p-value was less than 0.05.

Table 4.1(a). Initial selection of individuals

Age	Number of Individuals
Young adult (18-29 yrs)	11
Mid adult (30-49 yrs)	9
Older adult (50+ yrs)	11
Total	**31 individuals**

Table 4.1(b). Final selection of individuals

Age	Number of individuals
Young adult (18-29 yrs)	9
Mid adult (30-49 yrs)	6
Older adult (50+ yrs)	8
Total	**23 individuals**

Page 86 has been removed due to copyright restrictions. The information removed was Figure 4.1 (The location of the medieval village of Wharram Percy, Yorkshire, England. Beresford and Hurst , 1991).

Page 87 has been removed due to copyright restrictions. The information removed was Figure 4.2 (Anatomic orientation of the trans-iliac bone biopsy. Rao 1983).

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CHAPTER FIVE: PATTERNS OF CORTICAL AND TRABECULAR BONE LOSS IN A MEDIEVAL BRITISH SKELETAL SAMPLE

5.1. INTRODUCTION

Bone mass refers to the mineral quantity, specifically the bone mineral content (BMC) or density (BMD), of the skeleton (Hays, 2000). In contrast the term bone quality incorporates multiple interdependent measurements of skeletal strength, rigidity and micro-structural integrity (Burr, 1980; Burr et al., 1997; Turner and Burr, 1993; Vesterby, 1990). In contemporary populations, age-related decreases in the mineral quantity and micro-structural quality of the skeleton are frequently associated with the development of osteoporosis, a heterogeneous disorder characterized by severe skeletal atrophy, compromised skeletal strength and the increased occurrence of non-traumatic fractures in predominantly trabecular areas of the skeleton (Brickley, 2000; Heaney et al., 2000; Kholsa et al., 1995). It is the occurrence of these fractures which clinically distinguishes osteoporosis from its predecessor osteopenia, another metabolic bone disorder characterized by reductions in skeletal mass and quality but without fracture development (Ross, 1998).

Clinical investigators recognize several factors that causally contribute to bone loss and osteoporotic fracture risk in contemporary populations (Heaney et al., 2000; Kholsa et al., 1995; Tudor-Locke and McColl, 2000). These causal contributors, many of which are voluntary lifestyle choices, have also been examined from a paleopathological perspective with the reasoning that past peoples likely maintained lifestyles very different from those experienced by most modern-day inhabitants (Dequeker et al., 1997; Mays, 2000; Mays et al., 1998). These differences, in turn, may provide insight into which contributory factor(s) and/or lifestyle situation(s) predominate in the development and prevention of these multi-faceted diseases. However, many paleopathological investigations of both osteopenia and osteoporosis emphasize the quantitative and qualitative loss of cortical bone (e.g. Cho, 2000; Drusini et al., 2000; Mays, 2000; Mays, 1996; Rekewant, 1994), few studies evaluate aspects of diminished quantity and quality in trabecular tissues (e.g. Agarwal, 2000; Agarwal et al., 2004; Vogel et al., 1988). This emphasis occurs despite clinical evidence suggesting that reductions in both the quantity and microstructural quality of trabecular bone greatly contributes to osteoporotic fracture risk and development. Thus, given that quantitative and qualitative reductions in both cortical and trabecular bone influence the development of osteoporosis and that age is considered to be an etiological factor in the micro-architectural decline of trabecular bone in modern individuals (Britton and Davie, 1990; Parfitt et al., 1983), it is the objective of this research to examine the relationships among age, trabecular bone quality of the iliac crest, and cortical and trabecular bone quantity of the radius in a Medieval British skeletal sample.

5.2. MATERIALS AND METHODS

5.2.1. The materials

A skeletal sample of twenty-three females from the 10^{th}-16^{th} century peasant population of Wharram Percy (Yorkshire, England) was chosen for examination. Each of the selected individuals is female, of European ancestry, and falls into one of the following three age categories: young adult (18-29 years), mid adult (30-49 years), or older adult (50+ years) (Mays, 1996).

5.2.2. Measurement of bone quality

All measurements of trabecular bone quality were generated from the histomorphometric analysis of trans-iliac bone cores. This method was chosen for three reasons. First, current clinical study uses trans-iliac bone cores, or biopsies, as a preferred method for the structural assessment of osteoporosis and other metabolic bone diseases (Parfitt, 1992; Rao, 1983), and so by employing the same experimental protocol this research provides paleopathological data that is methodologically comparable to bone quality data generated from modern-day individuals. Second, the trans-iliac bone core, when compared to other methods of histomorphometric sampling, minimizes the tissue destruction of non-reproducible archaeological skeletal material and provides specimens with nominal architectural distortion thereby facilitating structural analysis (Foldes et al., 1995; Rao, 1983). Finally, if proven to be a reliable method for the structural assessment of trabecular bone in archaeological skeletal material, trans-iliac bone cores would provide yet another methodological option for bioarchaeologists interested in the examination of bone loss in past populations.

Collection of bone cores began by outlining a five centimeter isolateral inverted triangle on each innominate bone with the anterior superior iliac spine serving as a guide and the iliac crest border forming the base of the triangle (Rao, 1983). Bone cores measuring ten millimeters in diameter were then drilled from the center of this triangle using a diamond tipped plug-cutter inserted into a battery operated hand drill mounted on a portable drill press. With the exception of two individuals, who had cores drilled from both ilia for control purposes, each woman had one bone sample removed from either the right or left innominate. Factors that dictated which innominate was used included the presence and condition of the area to be sampled. Since no differences in bone mass or remodeling between the right and left iliac crest have been reported (Klein and Gunness, 1992), it was assumed that either side could be used for experimentation. Only those specimens that remained intact (i.e. had cortex on both sides of the core) were prepared and used in the ensuing analysis. All trans-iliac bone specimens were collected at Fort Cumberland, Portsmouth, England. Samples were then packaged and transported to laboratory facilities located at the University of Alberta, Edmonton, Canada where subsequent methodological procedures and analyses were conducted.

All specimens were cleaned in a solution of 70% ethanol and 30% distilled water, allowed to dry and then embedded cortical side up in an epoxy resin (#105) and hardener (#205) manufactured by West System®. Each specimen was then vacuum

impregnated for two to three minutes and, once removed from the vacuum, allowed to cure for at least 24 hours prior to sectioning. Thin sectioning was performed on an Isomet 11-1180 low speed saw, manufactured by Buehler Ltd. Specimens were mounted in a chuck and a thick section to the approximate center of the core was taken using a diamond wafering blade. Using the Isomet micrometer to ensure consistency in specimen thickness, three to five consecutive thin sections of 200-250 micrometers (μm) were then removed from the embedding block in accordance to the methodology recommended by Chappard and colleagues (1999). Although these sections are thicker than those found in some clinical studies (Chappard et al., 1999; Thomsen et al., 1998), Roberts and Wakely (1992) suggest that thick slices are preferable for trabecular bone due to the greater volume of material available for analysis. Once thin sectioning was complete, specimens were cleaned in ethanol and distilled water, allowed to dry and then mounted on slides using Permount. Specimens were digitally photographed at 7.5x magnification with a Nikon Coolpix 995 digital camera mounted on a WILD M5 macroscope.

The histomorphometric investigation of thin sections was performed using the image analysis program SigmaScan Pro 5.0. Digital images of the thin sections were first imported into SigmaScan. Prior to measurement, distance and area were calibrated using a "2-point" image calibration tool provided by the program. This tool converts the old distance and area measurements (pixels) into new, pre-defined measurement units (millimeters and millimeters squared). The calibration of each image pixel was derived from the digital photograph of a micrometry slide taken at 7.5x magnification. Once distance and area were calibrated, the trabecular architecture captured in each image was measured twice using a tracing tool provided by the program to select the desired area of interest. The two measurements were then averaged and used to calculate the following four structural parameters for each specimen (Chappard et al., 1999; Parfitt et al., 1987):

(i) Trabecular bone volume (BV/TV) (%) = trabecular bone area (no marrow spaces) x 100 / total trabecular bone area (including marrow spaces).

(ii) Average trabecular thickness (Tb.Th) (μm) = trabecular bone area / ½ perimeter of total area measured. To calculate the perimeter measurement, the demarcation between cortical and trabecular bone was made in accordance to a rule previously defined by Duncan (1973), which states that marrow spaces will be included within the perimeter measurement when the thickness of the trabeculae separating said space from the bone marrow cavity is equal to or less than half the radius of the space under question. The tracing tool was used to outline the marrow-bone interface, ensuring that the endosteal border of the cortex was not included in the perimeter measurement (Parfitt et al., 1983).

(iii) Trabecular number (Tb.N) (mm^2) = (BV/TV) / Tb.Th.

(iv) Trabecular separation (Tb.Sp) (μm) = 1000 / Tb.N - Tb.Th.

All calculations and nomenclature are in compliance with the ASBMR Histomorphometric Nomenclature Committee (Parfitt et al., 1987).

5.2.3. Measurement of bone quantity

All measurements of bone quantity, expressed as BMD (gm/cm^2), were previously collected by McEwan and colleagues (2004) using a QDR 4500A dual energy x-ray absorptiometry (DXA) machine to quantitatively assess the one-third, mid and ultra-distal sites of the radius (n=101). As described by McEwan and coworkers (2004), each radius was posteriorly aligned with the scanning table and placed in a plastic box with rice at a depth of 3 cm to act as a soft tissue substitute. The three sites, all of which are commonly employed in the clinical assessment of radial BMD (Bonnick, 2004), were automatically selected by the DXA machine on the basis of forearm length, with the one-third site located at the distance equal to 33% of forearm length and the ultra-distal site positioned 15 mm proximal to the end plate of the radius. The mid site is that region of interest (ROI) which falls between the one-third and ultra-distal sites. To check the repeatability of the DXA measurements, five radii were scanned ten times each with the bone removed and repositioned each time.

5.2.4. Statistical analysis

All statistical analyses were conducted using Microsoft Excel 2000. Descriptive statistics including sample mean, range, standard deviation, and standard error of the mean, were collected for each bone quality parameter measured. Correlations between age, BV/TV, Tb.Th, Tb.N and Tb.Sp, as well as those between the individual measurements of bone quality were examined. Additional correlations between each measurement of bone quality and quantifications of radial BMD at the one-third, mid, and ultra-distal sites were also calculated.

A one-way student's t-test was employed to determine statistical significance between (i) age and BV/TV, Tb.Th, Tb.N and Tb.Sp and (ii) each individual bone quality measurement. Statistical significance was observed when the p-value was less than 0.05.

5.3. RESULTS

Results from the analysis of age as a function of each trabecular bone quality measurement in the iliac crest are presented in Table 5.1 and expressed as mean +/- one standard deviation. As demonstrated, the females of this sample exhibit age-related changes in all four measurements of trabecular bone quality. Mean parameter measurements of trabecular bone volume (BV/TV), trabecular thickness (Tb.Th) and trabecular number (Tb.N) all reveal an age-related decrease, whereas trabecular separation (Tb.Sp) increases with age. However, only Tb.N demonstrates a statistically

significant decrease between the mid and older age categories ($p = 0.03$), while Tb.Sp displays a statistically significant increase between the same age groups ($p = 0.04$). Thus, a pattern of bone loss and increased trabecular separation is apparent from the young to mid to older age categories in this sample. It must be noted, however, that a great deal of overlap occurs between the quality measurements in each of these groups; suggesting that (i) the chosen measurements of bone quality vary considerably within, but not necessarily between, the different age categories (Fig. 5.1), and/or (ii) the small sample size has affected the results.

As determined by McEwan and colleagues (2004), bone mineral density (BMD) measurements taken at the one-third, mid and ultra-distal sites of the radius demonstrate an age-related decrease in bone quantity. However, only the BMD measurements from the older age group differ significantly from the younger age categories at all anatomical sites.

In addition to age, the relationship between the individual measurements of bone quality were also examined. Strong, positive linear correlations were found between BV/TV and the histomorphometric measurements of Tb.Th ($r = 0.946318$) (Fig. 5.2) and Tb.N ($r = 0.927661$). These findings suggest that as trabecular bone volume increases, so do the other two indicators of bone quality. In contrast, a negative non-linear correlation was found between BV/TV and Tb.Sp ($r = -0.931493$) (Fig. 5.3.), thus as trabecular bone volume decreases, the size of the marrow space separating individual trabeculae increases. Tb.Sp also demonstrates a strong, negative non-linear correlation with Tb.N ($r = -0.975221$) and, an albeit weaker one, with Tb.Th ($r = -0.835605$).

5.3.1. An interesting outlier

Throughout the analysis, a middle aged individual (G275) consistently demonstrated anomalous bone quality measurements relative to all other individuals in each of the age categories (Table 5.2). Radial BMD readings taken at the one-third, mid site, and ultra-distal sites of this individual were also higher than the mean averages for the young, middle and older age groups (McEwan et al., 2004) (Table 5.2). Further examination of these skeletal remains revealed an increased radial cortical index measurement combined with a corresponding reduction of the medullary cavity, increased density of the radial head, a slipped femoral capital epiphysis, periodontal disease and spondylolysis (McEwan et al., unpublished data). These findings suggest the possible presence of a pathological condition or conditions. Given this, G275 was removed from all subsequent analyses. For a further discussion of this individual, please refer to chapter six.

With the removal of G275, a change in the statistical significance of bone loss is apparent. Although the data continue to demonstrate an age-related decline in all bone quality measurements, statistically significant changes in BV/TV ($p = 0.016$), Tb.Th. ($p = 0.013$) and Tb.Sp. ($p = 0.02$), but not Tb.N, are evident between the young and middle aged individuals (Table 5.3). These results suggest that a substantial loss of trabecular bone volume and structure occurred by middle age, with non-significant decreases arising thereafter. Despite these losses, however, the hallmark osteoporotic fractures of the wrist and hip are completely absent from this sample. Although two individuals – a

young female (NA044) and an older female (G571) – exhibit fractures of the rib and vertebral bodies, their bone quality measurements are not abnormally deficient when compared to the parameter means of their respective age groups (Table 5.4). Given the small sample number, it is not possible to determine the statistical significance of this finding. However, Mays (1996) did observe these fracture types to be significantly associated with low cortical index measurements of the second metacarpal.

The comparison of each bone quality measurement and radial BMD at the one-third, mid, and ultra-distal sites revealed a weak positive correlation between these BMD measurements and BV/TV, Tb.Th. and Tb.N. In contrast, Tb.Sp demonstrated a negative correlation with each bone quantity measurement. Of the three radial sites quantified, the ultra-distal site most strongly correlated with each measurement of trabecular bone quality. This result is not surprising given that the ultra-distal site of the radius contains a large proportion of trabecular bone (55%) relative to amounts found at the one-third (5%) and mid (13%) radial sites (McEwan et al., 2004).

5.4. ASSESSMENT OF RESULTS AND DISCUSSION

5.4.1. Comparison of research findings with those from other related studies on the Wharram Percy skeletal sample

An advantage associated with the Wharram Percy skeletal collection for the purpose of this research is its use in previous studies on bone loss. In an examination of the trabecular architecture of the fourth lumbar vertebral body, Agarwal and colleagues (2004) assessed the bone quality of 54 individuals from this skeletal population. In addition to utilizing the quality measurements of trabecular bone volume, thickness, number and separation, these authors also measured strut analysis parameters and the anisotropic ratio of the bone. Their findings, summarily noted as a significant loss of trabecular bone structure between the younger (18-29 years) and middle (30-49 years) aged females, with no further decreases found between middle and older (50 + years) individuals, is generally comparable to the age-related patterns of bone loss seen in this research. Discrepancies between the two studies include: (i) the relationship between Tb.Th and age [non-significant in the Agarwal et al. research but significant in this study ($p = 0.01$)]; (ii) the relationship between Tb.N and age [significant between the young versus middle age categories of the Agarwal et al. study ($p = 0.011$) but not significant between the same parameters in this research ($p= 0.06$)]; followed by (iii) the statistically non-significant changes of bone quality observed between the mid and older aged females of this study as compared to no decreases (BV/TV, Tb.Th, and Tb.N) or increases (Tb.Sp) noted between the same parameters and age groups in the study of Agarwal and coworkers. Despite these discrepancies, however, both studies note a general trend of early onset trabecular bone loss. Although at odds with the patterning of loss generally found in contemporary female populations, this finding does suggest that the clinical association between structural indices of trabecular bone in the iliac crest and vertebral body (Klein and Gunness, 1992; Parfitt, 1992; Thomsen et al., 1998) is replicated in archaeological skeletal material.

The Wharram Percy skeletal collection has also been subjected to several studies investigating the quantity of bone in selected individuals. Agarwal (2001) found a significant decrease in vertebral BMD between the young and middle, but not the older, aged females, thereby reflecting the pattern of trabecular bone loss observed in this particular skeletal sample. However, the findings of McEwan and colleagues (2004), which were used for comparative purposes in this study, and those similarly noted by Mays and coworkers (1998) contrast with the results of Agarwal (2001). Through the examination of femoral BMD and cortical index, Mays and colleagues (1998) found a pattern of bone loss reflecting that observed in most modern populations, with the 30-49 year old females exhibiting significant age-related losses of BMD at the femoral neck and Ward's area. Given the age of occurrence, the authors suggest that this loss may be associated with the advent of menopause. A significant decrease of cortical bone was also found at the mid-shaft of the femur in the older females (50+ years), but this decrease was not attributed to the pre-menopausal loss of bone. In an earlier study examining the cortical index of the second metacarpal, Mays (1996) also found a significant decrease between younger (18-29 years) and older females (50+ years). That this deficit was more pronounced in the metacarpal than the mid-shaft of the femur led Mays and coworkers (1998) to suggest that the weight-bearing role of the latter may have factored into the maximization of cortical peak bone mass at this site.

Other factors may also account for the discrepant patterns of bone loss observed between the skeletal sites of this medieval population. Differences in the remodeling response of cortical versus trabecular tissues, specifically the increased activation frequency found in the latter, will lead to increased bone loss at trabecular sites if remodeling sequence becomes unbalanced (de Vernejoul, 1998; Mosekilde, 1999). Mays (1996), Mays and colleagues (1998) and McEwan and coworkers (2004) examined cortical or both cortical/trabecular sites, which could explain some of the disparate bone loss patterns noted between their studies and the research reported here. Methodological differences in the collection of data may also account for some of the discrepancies noted. For example, the use of radiographic images to determine the trabecular quality of vertebral sections was thought to contribute to the inaccurate measurement and differentiation of minor age and sex-related differences in trabecular thickness (Agarwal et al., 2004). This inaccuracy could explain some of the differences noted between the trabecular thickness measurements of this study and those of Agarwal and coworkers (2004). Finally, measurements of cortical thickness, bone mineral density and trabecular quality evaluate very different aspects of skeletal maintenance and can produce very different results in regards to fracture propensity (Agarwal et al., 2004), thus reinforcing the need to use several methods and both cortical and trabecular sites in order to systemically evaluate the overall health of the skeleton (Mosekilde, 1995).

5.4.2. Comparison of research findings with those from other archaeological skeletal samples

Few studies examining other archaeological skeletal populations have observed the early onset pattern of bone loss noted in this research. Utilizing DXA to

quantitatively assess the femoral BMD of a medieval Danish skeletal sample, Poulsen and colleagues (2001) found increased BMD values in the older (> 50 years) relative to the younger females. Likewise, through the measurement of femoral cortical thickness using Vernier sliding calipers, Dewey and coworkers (1969) observed patterns of premature cortical bone loss in their sampled Nubian females. This loss of femoral cortical thickness began by approximately twenty years of age and progressively declined with increasing age. Using the same Nubian skeletal population but employing microradiography to histologically evaluate the remodeling parameters of the femur, Martin and Armelagos (1985) also demonstrated a premature loss of cortical bone in the younger females (20-29 years) of their sample. However, these authors also noted a significant loss of bone in their older females (> 50 years), with the elderly women exhibiting increased rates of bone resorption and decreased bone mass.

Whereas numerous studies have noted that detrimental changes in the volume, density and structure of skeletal tissues are associated with increasing age (Brickley and Howell, 1999; Kneissel et al., 1997) and menopausal changes to osseous tissues (Kneissel et al., 1994; Mays, 2000), others have suggested that bone loss was not as problematic in past populations. For example, Lees and colleagues (1993) found the rates of both pre- and post-menopausal bone loss to be significantly greater in the proximal femur of modern women when compared to their 18^{th} to 19^{th} century females. Ekenman and co-workers (1995) also noted unusual discrepancies between the past and present, observing increased diaphyseal bone mineral density measurements in the lower extremities of their medieval Swedish sample when compared to contemporary controls. These authors did not observe trends suggestive of decreased bone mineral density in the older age groups (40-59 years) of either sex, indicating that both pre- and post-menopausal bone loss was not an issue for the women.

In contrast to the preceding two studies, the preservation of both pre- and post-menopausal bone was not replicated in this research. Although statistically significant changes in the trabecular bone volume and structure of the iliac crest were noted between the younger and middle aged females, non-significant changes in the histomorphometric parameters of BV/TV, Tb.Th, Tb.N and Tb.Sp and statistically significant diminutions of radial BMD were also observed between the middle and older age categories. These results suggest the presence of at least three patterns of bone loss in this sample. Whether or not these patterns were caused by etiologically distinct or inter-dependent risk factors remains to be determined.

5.4.3. Risk factors which may have causally contributed to the observed bone loss in the Wharram Percy sample

Several factors are known to causally contribute to bone loss and osteoporotic fracture risk in contemporary populations including: increasing age (Kholsa et al., 1995; Riggs and Melton, 1986), genetic predisposition (Nguyen et al., 2000; Rubin et al., 2000), "race" (Luckey et al., 1989; Pollitzer and Anderson, 1989); female reproductive history (Tudor-Locke and McColl, 2000) and a variety of lifestyle choices involving dietary intake and physical activity levels. Of particular interest to this researcher are those reproductive and lifestyle factors that likely contributed to differences in skeletal

health between past and present populations. For example, some clinical evidence suggests that cigarette smoking (Forsén et al., 1994; Jones and Scott, 1999; Law and Hackshaw, 1997) and the excessive intake of caffeine (Cooper et al., 1992; Nieves, 2002; Stini, 1995) and alcohol (Cheung et al., 1995; Heaney et al., 2000) can increase osteoporotic fracture risk among modern individuals. That tobacco and caffeine (in the form of coffee) were not available in England during medieval times would effectively eliminate these factors from consideration (Mays, 1996). However alcohol, in the forms of both ale and beer, would have been imbibed daily by medieval men, women and children as water was considered to be unhealthy for consumption during this time period (Bennett, 1987). Whether or not these individuals consumed enough alcohol (> 100 grams for adults) to detrimentally affect their attainment of peak bone mass and reduce their overall skeletal health is simply not known at this time (Mays, 1996).

5.4.3.1. Female reproductive history

Female reproductive history is another factor that may influence the patterns of bone loss observed in this skeletal sample. In clinical studies, several aspects of the female reproductive cycle have been scrutinized in regards to their effects on bone mass and structure. One of these factors is the age of menarche or the onset of menses. Although the findings are not universal, numerous cross-sectional studies have indicated that women who experienced early menarche (12.3 –12.6 years of age) exhibit increased BMD relative to those who began menstruating later (13.7-13.8 years) (Ito et al., 1995; Ribot et al., 1992; Rosenthal et al., 1989). Postulations as to why early menarche may be advantageous to female skeletal health include: an early exposure to the beneficial effects of estrogen, thereby maximizing peak bone mass (Tudor-Locke and McColl, 2000) and - if not interrupted by menstrual irregularities- an extended period influenced by the protective effects of this vital hormone (Fox et al., 1993; Ito et al., 1995).

Menarcheal age demonstrates a secular trend, declining in mean age over time (i.e. from 16 years of age in mid 19th century Western populations to approximately 13 years of age in contemporary societies) and from non-urban to urban living (Danker-Hopfe, 1986; Eaton et al., 1994; Sperling and Beyenne, 1997). The commencement of menses and the period of sub-fecundity which follows may also be influenced by sub-optimal nutrition and decreased fat mass accumulations (Danker-Hopfe, 1986; Jackes, 1994; Sharpe and Franks, 2002). In contrast, the onset of menopause is considered to be relatively stable over time, occurring at approximately fifty years of age with median values of forty to fifty years widely reported in many contemporary populations (Brincat et al., 1991; Mays, 1996; Pavelka and Fedigan, 1991). Documentary data gathered from medieval texts seem to confirm these findings during this time period (Post, 1971). Given the preceding evidence, it could be hypothesized that the rural women of Wharram Percy, when compared to contemporary females, experienced a later onset of menses but were of similar age at menopause. Hypothetically, this time frame could have minimized the accumulation of bone mass and effectively shortened the number of years in which these women's skeletons would be subjected to the protective effects of amplified estrogen levels. Additional periods of inadequate

nutrition, a common occurrence in medieval England, combined with the heavy workloads endured by most medieval peasant women (Bennett, 1987) could have led to decreased body mass and amenorheic or hypoestrogenic episodes (Sharpe and Franks, 2002), thereby contributing to the patterns of reduced bone quantity and quality seen in this skeletal sample.

Although plausible, an underlying assumption of the preceding hypothesis is that contemporary levels of circulating estrogen are "normal" or even beneficial to female skeletal health. However, several researchers suggest that the estrogen levels exhibited by many modern women may be abnormally high due to the increased numbers of menstrual cycles experienced during their fertile years (Eaton et al., 1994; Sperling and Beyenne, 1997; Weaver, 1998). Eaton and colleagues (1994) estimate that contemporary women in urban American societies will experience approximately 450 ovulations during their reproductive lifespan. In contrast, modern women living in foraging and non-western agricultural societies will experience between 50 to 160 lifetime ovulations [1](Eaton et al., 1994; Weaver, 1998). Although differences in the onset of menses and, to a lesser degree, menopause do exist between these groups of women, the most pronounced reproductive disparities lie in the number of pregnancies and the length of lactation (Eaton et al., 1994; Sperling and Beyenne, 1997).

Both pregnancy and lactation are high bone turnover states that can adversely affect the maternal skeleton through loss of bone mineral density and trabecular structure (Kalkwarf and Specker, 2002; Prentice, 2003; Reid, 2002). However, clinical evidence does indicate that complete recovery of bone lost during these reproductive phases can occur with the resumption of regular menstruation (Fox et al., 1993; Sowers, 1996). Indeed, some researchers speculate that increased parity may actually augment BMD in healthy women over time (Fox et al., 1993; Sowers, 1996). Thus, non-urban women, who have on average six children and breastfeed for approximately three to four years, as compared to 2.5 children and 3-6 months for their urban counterparts (Eaton et al., 1994; Sperling and Beyenne, 1997), should have higher BMD assuming good health. Additionally, the increased numbers of pregnancies and extended periods of lactation would effectively suppress 215 ovulations in non-urban women, minimizing the levels of circulating estrogen (Eaton et al., 1994). Lower estrogen levels have not only been associated with the decreased incidence of female reproductive cancers, specifically carcinomas of the breast, endometrium and ovaries (Eaton et al., 1994), but also with the diminution of menopausal symptoms such as hot flashes (Beyenne and Martin, 2001; Sperling and Beyenne, 1997). Weaver (1998) also suggests that decreased levels of estrogen throughout the reproductive life span of a woman may also minimize the dramatic effects of peri- and post-menopausal bone loss.

Menopause is primarily characterized by a decline in the circulating levels of estrogen (Marcus, 1994). Clinical investigators now suggest that osteoblastic bone forming cells are equipped with estrogen receptors and that these hormones prevent osteoblast apoptosis (Boyce et al., 2002). Weaver (1998) hypothesizes that these

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[1] Eaton and colleagues (1994:356) estimate the number of lifetime ovulations by subtracting the age at menarche from the age at menopause and multiplying by 13 ovulations per year. Pregnancy and periods of post-partum anovulation for each child are then subtracted from the potential maximum to arrive at lifetime ovulation estimates.

hormonal receptors may become "overly sensitized" in modern urban women due to the consistently high estrogenic exposure. Thus, once menopause occurs and these abnormally high levels of estrogen decrease, the apoptosis of osteoblastic cells and subsequent down-regulation of bone formation is intensified. This, when combined with the increased intensity and duration of osteoclastic bone resorption during the menopausal phases, would explain the exacerbated loss of osseous tissue experienced by many modern-day women (Jilka et al., 1992; Pacifici, 1998; Rodan et al., 1996).

Assuming that the reproductive characteristics of the Wharram Percy women would be more similar to those found in non-urban contemporary females, the hypothesis postulated by Weaver (1998) does effectively explain the gradual decrease in trabecular bone structure observed between the middle and older aged individuals of this skeletal sample. That statistically significant decreases in trabecular bone volume and thickness and increases in trabecular separation occurred between the younger and middle aged women may simply reflect a selective pattern of mortality – representing those women who died during pregnancy, immediately post-partum or during subsequent periods of lactation thereby preventing the recovery of bone lost during this reproductive period (Agarwal, 2001; Agarwal et al., 2004; Dewey et al., 1969; Martin and Armelagos, 1985; 1979; Poulsen et al., 2000). What this hypothesis does not explain, however, is the statistically significant decreases in radial BMD observed between the two younger groups and the oldest individuals of this sample (McEwan et al., 2004). Although these discrepant findings may simply reflect methodological differences, they could also imply site specificity in terms of the etiology of bone loss amongst these women. Thus while the structural quality of the iliac crest may be overtly influenced by the circulating levels of estrogen, the preservation of radial bone quantity may be dictated by other factors.

Another problem associated with this hypothesis is the presumption of increased parity and extensive lacteal periods among medieval peasant women. The ability to conceive, carry to term and nourish an infant for two or more years requires a certain level of fat mass accumulation and body weight (Frisch, 1988; Hart, 1993; Jackes, 1994; Sharpe and Franks, 2002; however see Ellison, 1994 for a criticism of this statement). Given the nutritionally restricted diet afforded to most medieval peasants combined with the frequent occurrence of crop failures, famines and pestilence (Campbell, 1995), one must wonder whether the health status of these women would have been sufficient to sustain the multiple pregnancies and prolonged periods of breastfeeding required to beneficially lower the levels of circulating estrogen.

5.4.3.2. Dietary intake

Although it is impossible to determine the precise nutritive quantity and quality of the diet at Wharram Percy, documentary evidence does suggest that the dietary intake of most medieval peasants was deficient in calcium, protein, vitamins A, C and D and calories (Gies and Gies, 2002). Calcium is, of course, vital to skeletal growth and maintenance, functioning in the formative accumulation of both skeletal quantity and quality and in the regulation of the body's metabolic processes (Goulding et al., 1998; Heaney, 2002; Nieves, 2002). The gastro-intestinal absorption and renal conservation of

calcium is controlled by many factors including levels of vitamin D (Halloran and Bikle, 1999; Matkovic, 1991; Vanderschuren and Bouillon, 1998). It has been suggested that the calcium intake at Wharram Percy would have been sufficient given that (i) cattle bones and pottery vessels used in dairying were found amongst the archaeological debris of the site suggesting that the occupants consumed milk and milk products and (ii) the site is located on chalk geology, thereby allowing ample levels of calcium to permeate the local water supply and foodchain (Mays, 1996). Indeed, clinical evidence indicates that the bioavailability of calcium from calcium rich mineral waters can be equivalent to that found in milk (up to 500 mg/liter) (Barclay, 2001) and, although unlikely that the women of Wharram Percy were drinking it directly, water was used during the processes of ale brewing and cooking (Bennett, 1987; McEwan, unpublished study).

Whereas the intake of calcium may have been adequate, insufficient levels of vitamin D have been noted in this skeletal population. Rickets, a vitamin D deficiency disease characterized by the overproduction and inadequate calcification of osteoid tissue (Dirckx, 2001), has been observed in some sub-adult remains at Wharram Percy (Lewis, 2002). This finding was not replicated among the adults (Mays, 1996). Other sub-adult skeletal indicators of stress at this site include: the presence of arrested longitudinal growth (Harris) lines, marked reductions in height, cortical thickness and index relative to contemporary subjects (Mays, 1999) and a high prevalence of sinusitis, acute trauma and respiratory infections (Lewis, 2002). These findings suggest that the children of Wharram Percy were highly susceptible to surrounding nutritive and environmental stresses (Mays, 1999). Thus, given the importance of optimal nutrition and vigor in the maximization of skeletal health (Heaney, 2002) and assuming that both nutritional and environmental stresses were relatively chronic throughout the medieval time period (Campbell, 1995), one must seriously question as to whether these individuals would have optimally attained their peak skeletal density and mass.

The significance of maximizing one's skeletal density and mass to decrease future osteoporotic fracture risk cannot be overstated. Using a computer generated model, Hernandez and colleagues (2003) estimated that a 10% increase in peak BMD can delay the development of osteoporosis in susceptible individuals by approximately 13 years. In contrast, a similar 10% change in the age at menopause or in the rates of non-menopausal bone loss will impede the onset of osteoporosis by only two years. Thus, these authors suggest that the attainment of an optimal peak BMD may be the single most influential factor in the prevention of this disease. In a study examining the radial peak cortical BMD of adults (n=106) and children (n=33) from Wharram Percy, McEwan (2003) determined that peak BMD at this skeletal site was attained by 35 years of age in both sexes, a finding very similar to that exhibited by many modern populations. Rates of bone mineral acquisition increased steadily from the sub-adult years through to young adulthood and osteoporotic fractures of the wrist and hip were not found in this skeletal population, suggesting that adequate, but not necessarily optimal, peak bone density was attained by most individuals.

Protein is another nutrient known to affect skeletal health, with the excessive consumption of animal protein resulting in the decreased renal absorption and increased urinary excretion of calcium and the diminishment of bone mass accumulations

(Abelow et al., 1992; Nieves, 2002). However, clinical data suggest that an inadequate intake of animal, but not plant, protein can also lead to the loss of bone, specifically declinations in the femoral, radial, and spinal BMD of elderly individuals (Hannan, 2001). Isotopic evidence gathered from Wharram Percy suggests a relatively uniform pattern of mixed food consumption, with protein contributions from both animal and plant resources (Richards et al., 2002). Whether or not the consumption of protein was adequate to meet daily requirements for skeletal health is not known; however, given the statistically significant decreases in femoral (Mays et al., 1998) and radial BMD (McEwan et al., 2004) noted in the older individuals of this population one must indeed question whether optimal amounts of protein were being consumed.

Although not featured as prominently in the clinical literature, insufficient consumption of vitamins A (retinol) and C can also have deleterious effects on skeletal health. Most commonly found in green vegetables, milk and milk products (McArdle et al., 1991), vitamin A profoundly influences bone growth and metabolism (Milstone and Leachman, 2001); whereas vitamin C – present in citrus fruits, peppers, broccoli, tomatoes and green leafy vegetables, is an essential cofactor for proper collagen formation (Nieves, 2002). Documentary evidence suggests that vegetables such as onions, leeks, garlic, cabbage, kale, turnips and parsnips were commonly consumed by the English medieval peasantry and it is possible that these food sources were available to the inhabitants of Wharram Percy (McEwan, 2003). However, given the restricted nature of the peasant diet combined with the episodic occurrences of famine throughout England during the early medieval time period (Campbell, 1995), it is likely that dietary nutrition and caloric values were diminished. Whether or not the amount of vitamins A and C consumed by these sampled individuals in any way contributed to the observed patterns of cortical and trabecular bone loss is not discernable. However, a reduction in the caloric intake of these women likely precipitated diminutions in body weight (Mays, 1996), a risk factor clinically associated with augmented rates of bone loss (Heaney and Matkovic, 1995; Hodgson, 2003).

5.4.3.3. Physical activity levels

Body weight is determined not only by caloric intake, but also by the level of caloric expenditure. Excessively low body weight reduces the mechanical loads borne by the skeleton and adversely influences circulating levels of the parathyroid hormone (PTH) (Bell et al., 1985; Heaney and Matkovic, 1995), thereby minimizing the tubular reabsorption of calcium and the renal production of 1,25 dihydroxyvitmain D_3 (Bell et al., 1985). Loss of menstrual regularity is also associated with excessive reductions in body weight and can result in estrogen-dependent bone loss (Drinkwater et al., 1990; Jackes, 1994; Kalkwarf and Specker, 1995; Schachter and Sloham, 1994). That the women of Wharram Percy expended a large number of calories daily is irrefutable since they were not only responsible for chores within the domestic sphere (i.e. gardening, dairying, weaving, and the tending of children and livestock), but also for agricultural tasks performed in the fields (Bennett, 1987; Goldberg, 1992; Mays, 1996). Skeletal evidence of this laborious lifestyle is provided by Derevenski (2000) in her analysis of activity-related osseous change in the spine of 59 males and females from Wharram

Percy. Noted similarities between the men and women of this sample in the patterning and distribution of spinal osteophytosis and apophyseal facet remodeling, pitting, eburnation and sclerosis suggest that the gender-specific division of labour was very fluid in this rural community. Thus it is quite likely that the women of Wharram Percy were regularly performing physically strenuous tasks. Although cross-sectional studies indicate that habitual physical activity typified by high impacts and heavy loads are beneficial for the male skeleton, excessive loading can decrease bone density and skeletal structure in females (Marcus, 1994; Stini, 1995). Whether the activities performed by these medieval women were sufficiently arduous to have adversely affected their skeletal fitness would, of course, be partially dependent upon their nutritive intake, body weight and overall health.

Despite the potentially negative effects of excessively arduous activities on the female skeleton, clinical evidence does indicate that a physically active lifestyle positively influences skeletal health via the mechanical loads borne by the skeleton (Heaney and Matkovic, 1995; Marcus, 1996). Optimal loading of skeletal tissues modulates the cellular activity of nearby bone remodeling units, increasing and decreasing the formative and resorptive functions of osteoblastic and osteoclastic bone cells (Lanyon, 1984; Heaney and Matkovic, 1995; Marcus, 1996). Augmented levels of physical activity have been correlated to increased cortical and trabecular BMD in both boys and girls (Forwood, 2001; Forwood and Burr, 1993; Kerr et al., 1996), thereby contributing to the maximization of their adult peak bone mass. Given these findings, it is plausible that the physically active lifestyle of medieval children would have enhanced their skeletal health.

Textual evidence implies that, health permitting, children in medieval peasant societies were vigorously active. Aside from play, children were considered to be significant factors in both the urban and rural labour force and were expected to perform age appropriate and, later, gender-specific tasks (Shahar, 1990).Work in the form of errand-running and the tending of smaller livestock (i.e. geese, pigs and sheep) began by approximately seven years of age, with the introduction of more strenuous tasks, such as weeding and the removal of stones and drawing of water, soon following (Shahar, 1990). At Wharram Percy, the analysis of sub-adult skeletal remains corroborates the preceding textual documentation. In an examination of linear and appositional long bone growth, Mays (1999) found beneficial increases in femoral cortical index and, to a lesser degree, cortical thickness between five to eight years of age. Mays tentatively associates these benefits with augmented levels of physical activity and ensuing increases in muscular strength.

Elevated levels of physical activity have also been shown to decelerate age – associated bone loss (Hodgson, 2003) and improve overall fitness, coordination, and muscular strength in the elderly thereby minimizing their future risk of falling and fracture (Nelson et al., 1994; Wickham et al., 1989). Several paleopathological analyses have attributed augmented activity levels to the minimization of age-associated bone loss in their skeletal samples (Ekenman et al., 1995; Lees et al., 1993; Vogel et al., 1988). Unfortunately, the older women of this study demonstrate a continued loss of both radial bone quantity and iliac bone quality; thereby indicating that an increasingly active lifestyle did not necessarily protect them against bone loss at these non-weight

bearing skeletal sites. However, as noted by McEwan and colleagues (2004), increased physical activity levels likely contributed to the absence of wrist and hip fractures in this sample and in the skeletal population as a whole. Since both of these fracture types are most commonly caused by falls (Hodgson, 2003), it could be postulated that the strenuous lifestyle of these women improved their overall coordination and muscular strength to such an extent that their risk of falling, and hence fracture, was greatly reduced.

The postulations of the preceding paragraph illustrate the benefits of examining "modern-day" disorders like osteoporosis from a paleopathological perspective. The results of this study support the clinical supposition that increased physical activity can reduce the risk of osteoporotic fracture in menopausal women (Hodgson, 2003). However, in this particular sample, it appears that the reduction in risk results not from the minimization of bone loss (i.e. due to optimal loading of the skeleton) but through the augmentation of muscular strength and coordination. Given this insight, it is recommended that programs aimed at the prevention of osteoporosis in the elderly incorporate core body exercises that improve balance, coordination and overall strength.

5.4.4. Comparison of research findings with those from modern clinical populations

For the most part, contemporary bone loss (osteopenia) and osteoporotic fracture risks are associated with increasing age (Kelly, 1999; Kholsa et al., 1995). Exceptions to this general trend include the presence of idiopathic and secondary causes resulting in the loss of bone (Kholsa et al., 1995; Reid and Harvey, 1997; Stini, 1990). Although osteopenia and osteoporosis do occur in both modern men and women, these disorders are usually more severe in the latter due to hormonally induced changes in skeletal mass and structure (Riggs et al., 1998). Indeed, several studies examining bone loss in the past have identified hormonally induced osseous tissue changes analogous to that found in contemporary female populations (Kneissel and colleagues, 1994; Mays, 2000). In this sample, the decreases in radial bone quantity (McEwan et al., 2004) and iliac bone quality observed between the middle aged and older women are probably indicative of menopausal changes to the skeleton. In contrast, the significant loss of trabecular bone volume, thickness and separation noted between the younger and middle aged females is likely attributable to secondary causes, specifically those associated with an inadequate nutrition, reproductive stresses and low body weight. Whether these secondary factors operated independently or simultaneously to effect the bone loss noted in this skeletal sample is not definitive; however given the multi-causal nature of bone loss, it is highly probable that a degree of inter-dependency exists among these etiological factors.

Despite the probable identification of menopausal bone loss in this sample, the incidence of osteoporotic wrist and hip fractures noted in many modern clinical populations is simply not replicated amongst the women of Wharram Percy. It is currently estimated that contemporary white women over 50 years of age have a 40% chance of sustaining a hip, wrist or spinal fracture during their lifetime (Hodgson, 2003). Although vertebral compression fractures were noted in this group, traumatic

but from the skeletal population as a whole. Several hypotheses have been put forth to explain the absence of these fracture types amongst the women of Wharram Percy. Mays (1996) suggests that, due to the lack of modern medical care, many of these women would not have survived long enough to sustain fractures of the hip. Current classification of osteoporotic trauma commonly associates hip fractures with type II, or senile osteoporosis; thus these fractures types are usually found in predisposed individuals over 70 years of age (Kholsa et al., 1995; Melton, 1995; Riggs and Melton, 1986; 1983). That some of these sampled women would have survived past fifty years is probable; but the occurrence of septa – and octogenarians in medieval British peasant societies was probably rare (Mays, 1996). While this reasoning feasibly explains the absence of hip fractures in this population, it does not account for the lack of osteoporotic wrist trauma since this fracture type commonly occurs between 51-75 years of age in clinical samples and is associated with type I or post-menopausal osteoporosis (Kholsa et al., 1995; Melton, 1995; Riggs and Melton, 1986; 1983).

Another explanation for the absence of hip and wrist fractures in this sample is the minimization of trauma associated with falling (Mays, 1996). In contemporary populations, both wrist and hip fractures are most commonly associated with falls to the ground (Kholsa et al., 1995; Lindsay, 1995; Melton, 1995; Stini, 1995). Causative factors contributing to these falls are usually associated with the aging process, specifically problems related to balance, declining vision, and overall weakness caused by the loss of bone, fat and muscle mass (Geusens et al., 2003; Hodgson, 2003). Elderly individuals are also more likely to have chronic medical conditions that may impede their ability to walk (i.e. stroke, Parkinson's disease, postural hypotension, or multiple sclerosis) and to be taking medications that affect their balance and/or cause dizziness (Geusens et al., 2003; Hodgson, 2003). Despite the hypothetical benefits provided by increased levels of physical activity, it is probable that the women of Wharram Percy experienced falls due to age-related declines in overall health. It is also possible that these women relied upon herbal remedies to relieve some of their age-associated symptoms and that these remedies may have impeded their balance and/or ability to walk. However when these women fell they would have most likely fallen upon impact absorbing surfaces such as grass, dirt and mud rather than the hard floors, pavement and concrete found in many modern day environments (Mays, 1996). Thus the impact-absorbing nature of the preceding medieval surfaces could help explain the absence of these fracture types in this skeletal population (Mays, 1996).

Finally, the apparent absence of hip and wrist fractures at Wharram Percy may simply reflect their non-detection. In modern clinical samples, almost one quarter of all individuals (50 + years) who sustain an osteoporotic fracture of the hip die within one year of the trauma (Hodgson, 2003). Given the lack of modern medical care, it could be reasoned that the onset of death in a similar situation would be comparable if not faster in past populations, thus complicating the identification of this fracture type. In archaeological skeletal samples the detection of peri-mortem fractures, or those breaks that occur close to death thus exhibiting minimal osseous evidence of healing, are extremely difficult to distinguish from post-mortem skeletal damage (Brickley, 2002). Adding to the difficulty is the inherent fragility of osteoporotic remains due to the decreased bone mineral content and diminished micro-architectural integrity of the

tissue, thereby increasing its susceptibility to damage during burial, excavation, recovery and processing (Brickley, 2002; Walker, 1995). However, extensive investigations of the Wharram Percy skeletal remains by Mays (1996) and McEwan and colleagues (2004) suggest that osteoporotic fractures of the hip and wrist were not present in this population and thus their absence seems to represent a real phenomenon.

5.5. CONCLUSIONS

The examination of both cortical and trabecular bone quantity and quality in a medieval British skeletal sample has revealed three distinct patterns of age-related reductions in bone mass and structure. The first of these patterns is one of early onset bone loss - with statistically significant decreases in trabecular bone volume and thickness and increases in trabecular separation evident between the young and middle-aged women of this skeletal sample. Although infrequent in clinical populations, this premature patterning of female bone loss has been observed in several archaeological samples (Agarwal, 2001; Agarwal et al., 2004; Dewey et al., 1969; Martin and Armelagos, 1985; Poulsen et al., 2001). It is postulated that these significant losses are attributable to secondary causes, specifically those associated with inadequate nutrition, reproductive stresses and low body weight. Whether these secondary factors operated independently or simultaneously to effect the bone loss noted in this skeletal sample is not definitive; however given the multi-causal nature of bone loss, it is highly probable that a degree of interdependency exists among these etiological factors.

In contrast, the other two patterns can be identified by bone loss between the middle-aged and older women of this sample , specifically statistically significant decreases in radial bone quantity (McEwan et al., 2004) and non-statistically significant changes in iliac bone quality. It is hypothesized that these bone loss patterns are indicative of menopausal changes to the skeleton. Despite this diagnosis, however, the women of Wharram Percy do not exhibit symptomatic fractures of the wrist or hip– features typical of osteoporosis. Although impact-absorbing surfaces may be a factor, this finding does support the clinical supposition that strenuous physical activity reduces the risk of osteoporotic fracture in menopausal women (Hodgson, 2003) and demonstrates how the examination of "modern-day" disorders from a paleopathological perspective can offer insight into which contributory factors predominate in the prevention of multi-faceted diseases.

Table 5.1. Measurements of trabecular bone quality [1]

Age	n	BV/TV (%)	Tb.Th (μm)	Tb.N (mm^2)	Tb.Sp (μm)
Young	10	43.74 +/- 7.18	264.82+/- 26.02	1.65 +/- 0.15	347.36 +/- 70.88
Mid	7	40.31 +/- 14.49	251.27 +/- 49.51	1.57 +/- 0.24	397.55 +/- 134.45
Old	8	31.51 +/- 10.58	233.27 +/- 38.30	1.32 +/- 0.25	551.15 +/- 193.85
$p < 0.05$		ns	ns	mid vs. old	mid vs. old

[1] Age groups are categorized as: young (18-29 years); mid (30-49 years); old ($\geq$ 50 years). "n " refers to numbers of specimens. BV/TV – trabecular bone volume, Tb.Th – trabecular thickness, Tb.N – trabecular number, and Tb.Sp - trabecular separation. Statistically significant differences between age groups are designated by $p < 0.05$ level with a one-tailed student's t-test. Results are expressed as mean +/- one standard deviation.

Table 5.2. Comparison of G275 bone quality and quantity measurements to the young, mid and adult means [1]

Bone Quality	**G275 n = 1**	**Young Adult Mean n = 10**	**Mid Adult Mean n = 6**	**Old Adult Mean n = 8**
BV/TV (%)	69.90	43.74	35.37	31.51
Tb.Th (μm)	353.75	264.82	234.19	233.27
Tb.N (mm^2)	1.97	1.65	1.50	1.32
Tb.Sp (μm)	152.29	347.36	438.43	551.15
Bone Quantity	**G275 n = 1**	**Young Adult Mean n = 5**	**Mid Adult Mean n = 5**	**Old Adult Mean n = 7**
1/3 site (gm/cm^2)	0.781	0.716	0.713	0.567
Mid site (gm/cm^2)	0.707	0.58	0.588	0.475
Ultra-distal site (gm/cm^2)	0.676	0.529	0.496	0.381

[1] Age groups are categorized as: young (18-29 years); mid (30-49 years); old (≥ 50 years). "n " refers to number of specimens. Bone quality measurements include: BV/TV – trabecular bone volume, Tb.Th – trabecular thickness, Tb.N – trabecular number, and Tb.Sp - trabecular separation. Bone quantity refers to measurements of bone mineral density at the one-third, mid and ultra-distal sites of the radius (McEwan et al., 2004). The mid adult mean does not include the bone quality and quantity measurements of the individual G275.

Table 5.3. Measurements of trabecular bone quality without the inclusion of individual G275[1]

Age	n	BV/TV (%)	Tb.Th (μm)	Tb.N (mm^2)	Tb.Sp (μm)
Young	10	43.74 +/- 7.18	264.82+/- 26.02	1.65 +/- 0.15	347.36 +/- 70.88
Mid	6	35.37 +/- 6.90	234.19 +/- 22.15	1.50 +/- 0.18	438.43 +/- 87.50
Old	8	31.51 +/- 10.58	233.27 +/- 38.30	1.32 +/- 0.25	551.15 +/- 193.85
$p<0.05$		young vs. mid	young vs. mid	ns	young vs. mid

[1] **Age groups are categorized as: young (18-29 years); mid (30-49 years); old (≥ 50 years). "n " refers to numbers of specimens. BV/TV – trabecular bone volume, Tb.Th – trabecular thickness, Tb.N – trabecular number, and Tb.Sp - trabecular separation. Statistically significant differences between age groups are designated by $p < 0.05$ level with a one-tailed student's t-test. Results are expressed as mean +/- one standard deviation.**

Table 5.4. Comparison of bone quality measurements between individuals with fractures (NA044 and G571) and the young and older aged sample means of those without fractures[1]

Bone Quality	NA044 n = 1	Young Adult Mean n = 9	Young Adult Range n = 9	G571 n = 1	Old Adult Mean n = 7	Old Adult Range n = 7
BV/TV (%)	40.23	44.13	33.28 – 58.82	40.83	30.18	18.07 – 49.34
Tb.Th (μm)	248.14	266.67	224.09 – 309.08	258.46	229.67	184.87 – 301.21
Tb.N (mm^2)	1.62	1.65	1.39 – 1.90	1.57	1.28	0.98 – 1.64
Tb.Sp (μm)	368.69	344.98	216.40 – 478.84	374.47	576.39	309.25 – 837.88

[1] **Age groups are categorized as: young (18-29 years) and old (≥ 50 years). "n " refers to numbers of specimens. BV/TV – trabecular bone volume, Tb.Th – trabecular thickness, Tb.N – trabecular number, and Tb.Sp – trabecular separation.**

Figure 5.1. Trabecular bone volume, thickness, number and separation as a function of age. Note the large degree of overlap between the age categories, suggesting that the measurements of bone quality vary considerably within, but not necessarily between the groups. "n" refers to the number of specimens.

Fig. 5.1a. Trabecular Bone Volume as a Function of Age

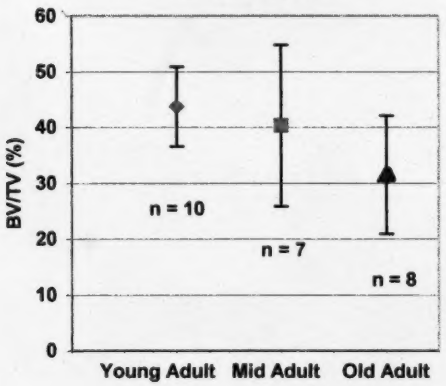


Fig. 5.1b. Trabecular Thickness as a Function of Age

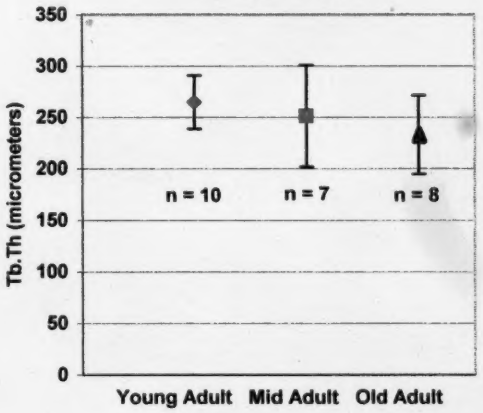


Fig. 5.1c. Trabecular Number as a Function of Age

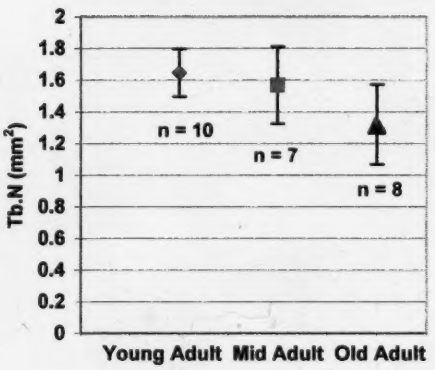


Fig. 5.1d. Trabecular Separation as a Function of Age

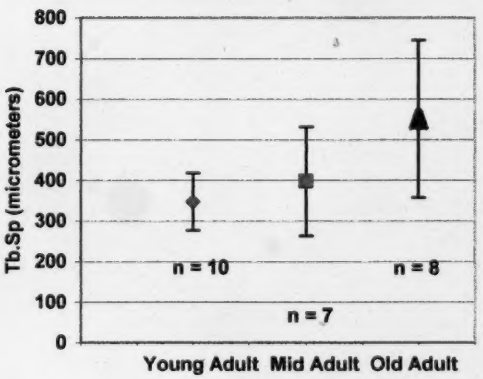


Figure 5.2. Trabecular Bone Volume as a Function of Trabecular Thickness

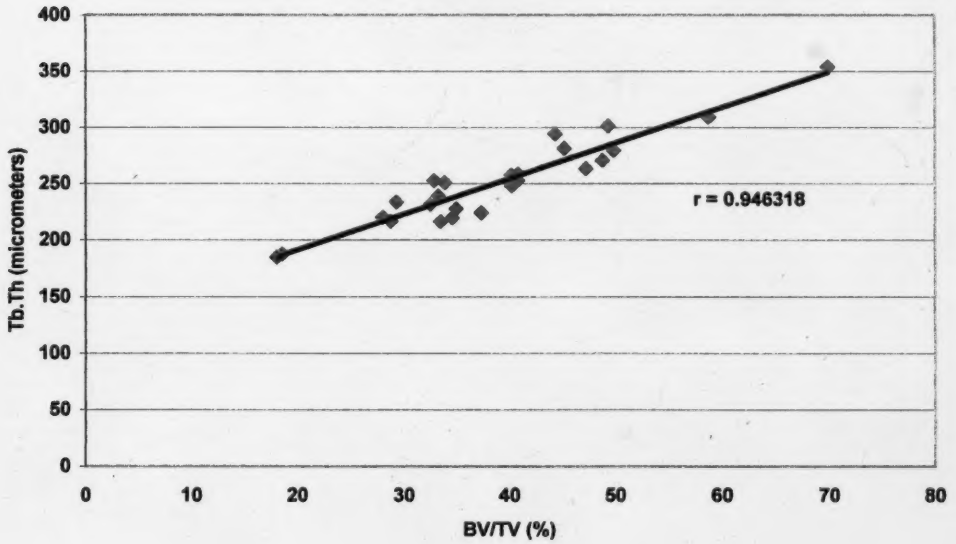
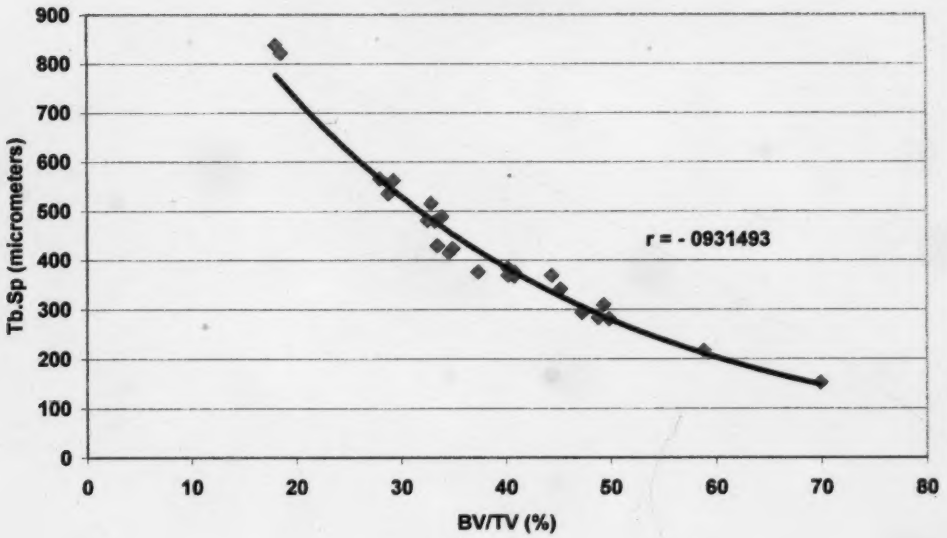


Figure 5.3. Trabecular Bone Volume as a Function of Trabecular Separation



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CHAPTER SIX: A PALEOPATHOLOGICAL EXAMPLE OF RENAL OSTEODYSTROPHY IN A MEDIEVAL BRITISH SKELETAL SAMPLE[1]

6.1. INTRODUCTION

Archaeological excavations carried out at the deserted medieval village site of Wharram Percy (Yorkshire, England) resulted in the recovery of 687 articulated human skeletons, 358 of which were adults (Beresford and Hurst, 1990; Mays et al., 2001; Mays, 1996). The burials, many of which were found in the churchyard of the site, date primarily to the 10^{th}-16^{th} centuries AD and are thought to belong to ordinary peasants who either lived within the village of Wharram Percy itself or in one of four other townships associated with this rural parish (Hurst, 1984; Mays et al., 2001). Due to the excellent preservation of these skeletal remains and the large number of older adults (n=119) found within the sample, this collection has been employed in numerous studies examining paleopathological patterns of age-associated bone loss (Agarwal, 2001; Agarwal et al., 2004; Mays, 1996; Mays et al., 1998; McEwan et al., 2004). The most recent investigation of this kind evaluated the age-associated decline of trabecular bone volume and structure in the iliac crest of twenty-three females. In this study, bone cores measuring ten millimeters in diameter were extracted from a clinically recommended site on the ilium and the histomorphometric parameters of trabecular bone volume (BV/TV), thickness (Tb.Th), number (Tb.N) and separation (Tb.Sp) were examined. The findings of this examination, when combined with data collected by other investigators (McEwan et al., 2004; McEwan et al., unpublished data) suggest the presence of an interesting outlier, a 25-35 year old female identified as G275.

6.2. INDIVIDUAL G275

Dentally assessed age-at-death estimates and the determination of sex using standard osteological procedures were previously performed by Mays (1996). Since discrepancies with these initial assessments were not noted, the original determinations were used in this analysis. Qualitative evaluations of iliac bone structure revealed that this individual had dramatically increased measurements of trabecular bone volume (BV/TV), thickness (Tb.Th), number (Tb.N) and separation (Tb.Sp) relative to all other examined individuals. Radial bone mineral density (BMD) measurements taken at her one-third, mid, and ultra-distal sites were also higher than the mean averages for the young, middle and older aged females of this sample (McEwan et al., 2004). Further examinations of G275 revealed increased cortical index measurements combined with corresponding reductions in the medullary cavity of the radius, increased density of the radial head, a slipped femoral capital epiphysis, periodontal disease and spondylolysis (McEwan et al., unpublished data). The combination of these findings suggest the presence of a potentially pathological condition.

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[1] A version of this chapter has been presented as a poster at the 15^{th} Annual Paleopathology Association European Meeting, Durham, U.K. McEwan JM, Rossi D and Mays S (2004).

6.3. DIFFERENTIAL DIAGNOSIS

In a poster differentially diagnosing the pathology of individual G275, McEwan and colleagues exclude the following conditions:

(i) Hypoparathyroidism: a metabolic disorder caused by the failure of the parathyroid glands to secrete sufficient amounts of biologically active parathyroid hormone (PTH) (Levine, 1998). This failure results in hypocalcemia, hyperphosphatemia and, in individuals with a longstanding affliction, significantly increased bone mineral density (Levine, 1998). However, clinical hypoparathryoidism is frequently the result of glandular surgery or radical operations involving the removal of laryngeal and esophageal carcinomas (Levine, 1998), procedures which would likely not have occurred during medieval times.

(ii) Osteopetrosis: or "marble bone disease" is a generic term which labels a group of disorders characterized by the pathogenic diminishment of osteoclastic cell function (Whyte, 1998). Distinguishing features of these disorders include: (a) deficient periosteal and endosteal resorption resulting in osteosclerosis of trabecular tissues, cortical hyperostosis, and reduction of marrow cavities, (b) manifestation of alternating dense and lucent bands in the long bones and pelvis, (c) widening of the appendicular metaphyses and (d) transverse fracturing of the long bones (Adler, 2000; Whyte, 1998). Benign type I is also associated with the increased radiodensity of skeletal elements, specifically the skull (Whyte, 1998). Although individual G275 exhibits increased bone mineral density and trabecular thickening combined with a reduction of marrow spaces in both the radius and iliac crest (Figure 6.1.), she does not present evidence of metaphyseal widening, sclerotic banding of the pelvis and/or long bones, or transverse pathological fractures.

(iii) Progressive Diaphyseal Dysplasia: or "Camurati-Englemann" disease is a rare developmental disorder inherited as an autosomal dominant trait (Whyte, 1998). Radiological features include: cortical hyperostosis of long bone diaphyses and proliferation of new bone on both the periosteal and endosteal surfaces (Whyte, 1998). In severely afflicted children, these new bone proliferations are frequently accompanied by osteopenia (Whyte, 1998). Commonly affected skeletal elements include the tibiae and femora followed by the arm bones, vertebrae, skull, scapulae, clavicles and, occasionally, the pelvis (Whyte, 1998). Although the radius of G275 exhibits significantly increased cortical bone index measurements relative to other individuals in her age group (McEwan et al., unpublished data), the total diaphyseal width of her radius is normal thus indicating that pathological bone proliferation and widening of the shaft did not occur. Additionally, G275 is not osteopenic as demonstrated by BMD measurements taken at the one third, mid and ultra-distal sites of her radius (McEwan et al., 2004). Finally, given the rarity of Camurati-Englemann disease in modern populations [approximately 100 cases have been reported in the clinical literature (Whyte, 1998)], there is but a minute probability that G275 was afflicted with this disorder.

With the exclusion of the preceding pathological possibilities, McEwan and colleagues suggest that the skeletal evidence from G275 is indicative of renal osteodystrophy – a broad term used to describe skeletal disorders resulting from chronic renal impairment and failure (Slatopolosky and Delmez, 1998). In this case, McEwan and colleagues hypothesize that a progressive polycystic disease impaired renal functions, thereby resulting in the development of secondary hyperparathyroidism and the subsequent abnormalities noted in the cortical and trabecular tissues of this individual. Renal osteodystrophy may take several forms including: (i) osteitis fibrosa – a disorder demonstrating increased osteoclastic resorption of calcified bone and replacement by fibrous tissue; (ii) osteomalacia – a disease characterized by the under-mineralization of osteoid due to vitamin D deficiencies; and (iii) osteoscleorosis – a skeletal condition distinguished by increased thickness and numbers of trabeculae combined with the radiographic occurrence of densely woven bone at the vertebral endplates (Andreoli et al., 1986; Slatopolosky and Delmez, 1998). The highly dense bone of the endplates contrasts with that vertebral body, accounting for the "rugger jersey" appearance of the spine (Andreoli et al., 1986; Slatopolosky and Delmez, 1998). Although all of the preceding forms may clinically present in a single patient, usually one form will predominate (Andreoli et al., 1986). In individual G275, it appears that osteosclerosis is the predominate form given the augmented BMD and histomorphometric measurements of trabecular tissue at both the radius and iliac crest and the "rugger jersey" appearance of the vertebrae (McEwan et al., unpublished data).

6.4. DISCUSSION

The probable identification of renal osteodystrophy in individual G275 demonstrates the pitfalls associated with the non-detection of pathological conditions in sampled individuals. The results from the histomorphometric examination of trabecular bone quality and structure in the iliac crest were presented in Chapter Five in such a way as to demonstrate the effects that a single pathological individual can have on the data. When individual G275 was included in the analysis, statistically significant differences between trabecular number and separation were noted only between the middle and older aged individuals (Table 6.1.). In contrast, with the removal of individual G275 statistically significant losses of trabecular bone volume and structure were observed by middle age with minimal decreases arising thereafter (Table 6.1.). These disparate patterns of bone loss would have resulted in very different interpretations of the data, thus illustrating the importance of utilizing multiple diagnostic techniques on both cortical and trabecular skeletal sites to identify aberrant individuals.

6.5. CONCLUSIONS

This short chapter presents the combined efforts of several investigators in the probable identification of renal osteodystrophy in a medieval British skeletal sample. It is hypothesized that a progressive polycystic disease impaired the renal functions of this middle-aged female, resulting in the development of secondary

hyperparathyroidism and the subsequent abnormalities noted in both her cortical and trabecular bone tissues. This chapter also highlights the effects that a single individual can have on paleopathological data and stresses the importance of utilizing multiple diagnostic techniques on both cortical and trabecular bone to identify aberrant individuals.

Table 6.1a-d. Measurements of trabecular bone quality with and without the inclusion of individual G275[1]

(a) Measurements of trabecular bone volume (BV/TV)

Age	n	BV/TV (%) with G275	BV/TV (%) w/o G275
Young	10	43.74 +/- 7.18	43.74 +/- 7.18
Mid	7	40.31 +/- 14.49	35.37 +/- 6.90
Old	8	31.51 +/- 10.58	31.51 +/- 10.58
$p < 0.05$		ns	young vs. mid

(b) Measurements of trabecular thickness (Tb.Th)

Age	n	Tb.Th (μm) with G275	Tb.Th (μm) w/o G275
Young	10	264.82+/- 26.02	264.82+/- 26.02
Mid	7	251.27 +/- 49.51	234.19 +/- 22.15
Old	8	233.27 +/- 38.30	233.27 +/- 38.30
$p < 0.05$		ns	young vs. mid

(c) Measurements of trabecular number (Tb.N)

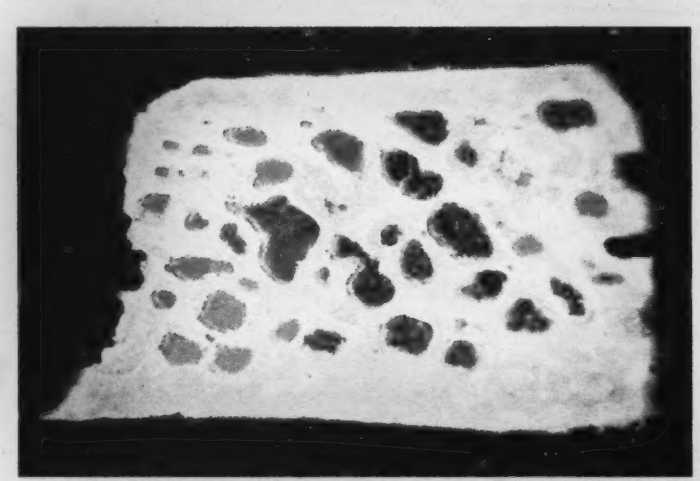
Age	n	Tb.N (mm^2) with G275	Tb.N (mm^2) w/o G275
Young	10	1.65 +/- 0.15	1.65 +/- 0.15
Mid	7	1.57 +/- 0.24	1.50 +/- 0.18
Old	8	1.32 +/- 0.25	1.32 +/- 0.25
$p < 0.05$		mid vs. old	Ns

(d) Measurements of trabecular separation (Tb.Sp)

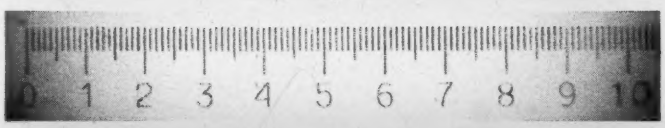
Age	n	Tb.Sp (μm) with G275	Tb.Sp (μm) w/o G275
Young	10	347.36 +/- 70.88	347.36 +/- 70.88
Mid	7	397.55 +/- 134.45	438.43 +/- 87.50
Old	8	551.15 +/- 193.85	551.15 +/- 193.85
$p < 0.05$		mid vs. old	young vs. mid

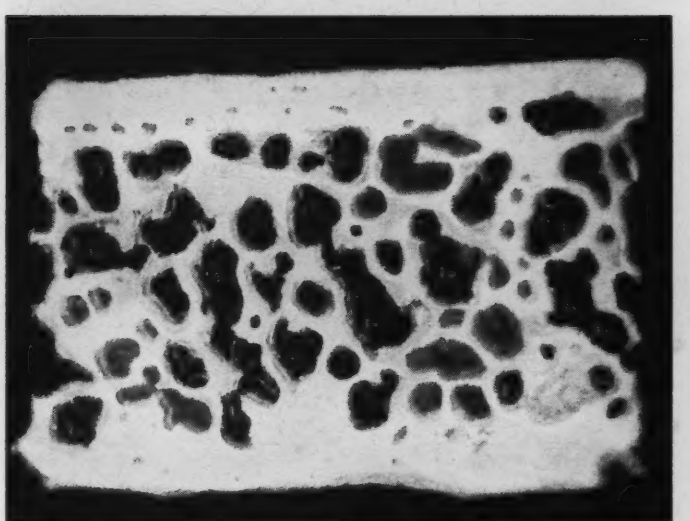
[1] Age groups are categorized as: young (18-29 years); mid (30-49 years); old ($\geq$ 50 years). "n " refers to numbers of specimens. Statistically significant differences between age groups are designated by $p < 0.05$ level with a one-tailed student's t-test. Results are expressed as mean +/- one standard deviation.

Figure 6.1. Iliac thin sections belonging to individual G275 (top) and another middle-aged female, individual V61 (bottom). Note the increased thickness of trabeculae and the reduced numbers and size of the marrow spaces exhibited by G275 when compared to V61. Digital images of ten millimeter cores taken at 7.5x magnification. (BV/TV – trabecular bone volume; Tb.Th. – trabecular thickness; Tb.N. – trabecular number; Tb.Sp. – trabecular separation[1])



(a) Iliac bone quality measurements of individual G275: BV/TV – 69.90% ;Tb.Th. – 353.75μm; Tb.N. – 1.97mm^2; Tb.Sp. – 152.29μm [1]





(b) Iliac bone quality measurements of individual V61: BV/TV – 28.80%; Tb.Th. – 270.48μm; Tb.

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CHAPTER SEVEN: A TECHNICAL NOTE ON THE UTILITY OF TRANS-ILIAC BONE CORES IN THE HISTOMORPHOMETRIC EXAMINATION OF ARCHAEOLOGICAL SKELETAL MATERIAL

7.1. INTRODUCTION

Osteopenia and osteoporosis are heterogeneous disorders characterized by reductions in both the mineral mass and microarchitectural quality of the skeleton (Avioli and Kleerekoper, 1998; Kanis, 1996; Ross, 1998). In clinical populations, the detection and diagnosis of these diseases is frequently performed through the non-invasive quantification of bone mineral mass or density (BMD) (Hays, 2000). Several paleopathological examinations of bone loss have emulated these clinical studies by employing similar diagnostic techniques to successfully measure the bone mineral mass and density of past peoples (Agarwal, 2001; Foldes et al., 1995; Kneissel et al., 1994; Lees et al., 1993; Mays et al., 1998; McEwan et al., 2004; Poulsen et al., 2001). However, the assessment of both osteopenia and osteoporosis in contemporary populations has revealed considerable overlap in BMD measurements between individuals with and without fractures, thus indicating that bone density is not the only factor determining osteoporotic fracture risk (Aaron et al., 2000; Audran et al., 2001; Hahn et al., 1992; Legrande et al. 2000; Thomsen et al., 1998). Instead, clinicians are now emphasizing the importance of bone quality (Schnitzler, 1993; Thomsen et al., 1998) – a broad term which incorporates measurements of skeletal remodeling, biomechanical resiliency and micro-architectural structuring of trabecular bone (Burr, 1980; Lundon and Grynpas, 1993; Turner and Burr, 1993). A clinical method commonly employed to evaluate the latter is the histomorphometric analysis of trans-iliac bone biopsies.

Taken from the iliac crest, the trans-iliac bone biopsy is the preferred *in vivo* method for the structural assessment, diagnosis and management of osteoporosis and other metabolic bone diseases (Klein and Gunness, 1992; Parfitt, 1992; Rao, 1983). The procedure is considered not only practical because the site is easily accessible and causes minimal discomfort to the patient, but also provides specimens which are architecturally similar to the vertebral body – a skeletal site which is particularly prone to osteoporotic fracture in both men and women (Klein and Gunness, 1992; Parfitt, 1992; Thomsen et al., 1998; however see Cho, 2002; Compston et al., 1987 and Britton and Davie, 1990 for criticisms of this statement). Researchers have also found significant correlations between the histomorphometry of the iliac crest and BMD measurements of the spine (Delmas et al., 1998) and radius (Hesp et al., 1991).

Whereas several investigators have utilized the iliac crest (Foldes et al., 1995; Vogel et al., 1988) to evaluate bone loss in past populations, only a few have employed trans-iliac bone cores (biopsies)[1] (Cho, 2002; Weinstein et al., 1988). In the latter study (Weinstein et al., 1988), a trephine drill was used to create the required core. However,

[1] A biopsy is the process of removing tissue samples from living individuals. Given that a skeletal sample was used for the purposes of this study, the term "biopsy" was replaced with "core".

given that this instrument was not available for this study, the objectives were: (i) to find an alternate method to viably and inexpensively extract the required bone cores, and (ii) to determine the methodological feasibility of utilizing these cores in the histomorphometric examination of trabecular bone quality in archaeological skeletal material.

7.2. MATERIALS AND METHODS

A skeletal sample consisting of twenty-three individuals from the medieval peasant population of Wharram Percy (Yorkshire, England) was selected for examination. Each individual is female, of European ancestry, and falls into one of the following three dentally determined age categories: young adult (18-29 years), mid adult (30-49 years) and older adult (50+ years) (Mays, 1996). Bone cores measuring ten millimetres in diameter were extracted from a clinically recommended site on the ilium using a diamond tipped plug-cutter inserted into a battery operated hand drill mounted on a portable drill press. Only those cores that retained cortices on both sides were considered viable and used in the ensuing analysis. Selected cores were embedded in an epoxy resin and thin sectioned using an Isomet 11-1180 low speed saw. In accordance to the method suggested by Chappard and colleagues (1999), three to five consecutive thin sections measuring 200-250 micrometers were removed from each embedding block parallel to the long axis of the core. Specimens were cleaned in ethanol and distilled water, dried, mounted on slides using Permount and photographed at 7.5x magnification with a Nikon Coolpix 995 digital camera mounted on a WILD M5 macroscope. The histomorphometric evaluation of trabecular bone quality was performed using the image analysis program SigmaScan Pro 5.0 to determine the following four parameters: (i) trabecular bone volume, (ii) trabecular thickness, (iii) trabecular number and (iv) trabecular separation.

7.3. RESULTS AND DISCUSSION

The results of this study demonstrate that both the chosen method of extraction and the utilization of trans-iliac bone cores in the qualitative evaluation of archaeological skeletal material is methodologically feasible. Of the thirty-one females initially selected for examination, trans-iliac bone cores were successfully removed from twenty-three (74%) of these individuals. Exclusion of a specimen from subsequent histomorphometric analyses was most often due to separation of the cortex from the core – an unfortunate side effect of drilling those skeletal remains that were somewhat fragile. Despite the preceding problem this method not only minimized the destruction of skeletal tissue surrounding the successfully sampled bone cores, but also provided specimens with nominal architectural distortion thereby facilitating the structural analysis of the bone (Figure 7.1).

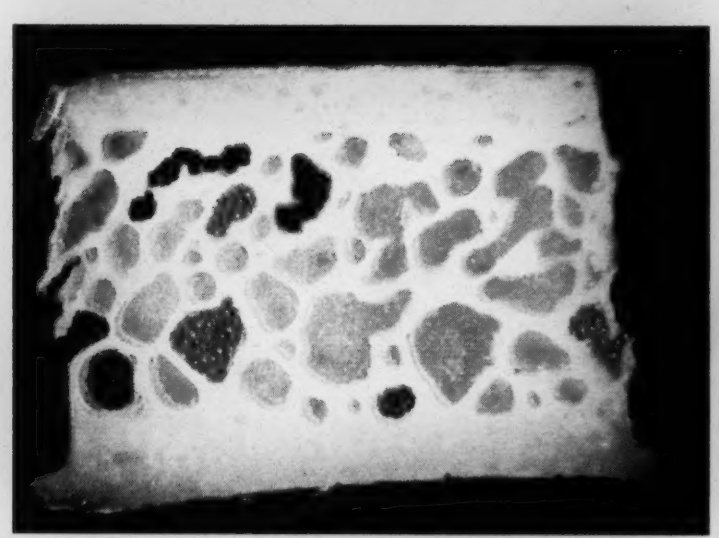
The ensuing histomorphometric analyses of the trans-iliac bone cores revealed a substantial loss of trabecular bone volume and structure between the younger and middle aged females of this sample, with non-significant decreases arising thereafter. Considering several risk factors known to causally contribute to bone loss and

osteoporotic fracture risk in contemporary populations, it is postulated that the qualitative reductions observed between the mid and older women of this sample are indicative of menopausal changes to the skeleton. In contrast, the significant bone loss noted between the young and middle aged individuals is likely attributable to secondary causes, specifically those associated with inadequate nutrition, reproductive stresses and low body weight.

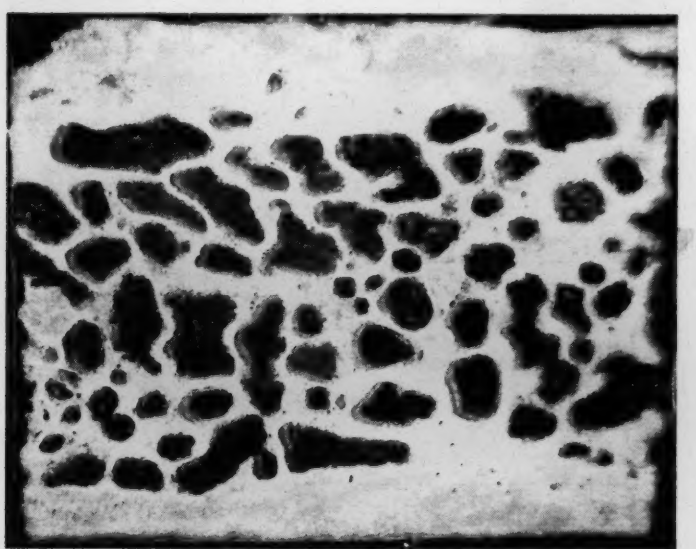
7.4. CONCLUSIONS

The results of this study indicate that the use of a plug cutter and battery operated hand drill for the extraction of trans-iliac bone cores and the employment of these cores in the qualitative evaluation of archaeological skeletal material is methodologically feasible. The positive results of this study indicate yet another procedural option available to bioarchaeologists interested in the examination of bone loss in past populations.

Figure 7.1. Digital images of trans-iliac bone cores measuring ten millimeters in diameter (7.5x magnification). Note that the thin sections exhibit minimal distortion of the trabecular microarchitecture, thereby permitting the required histomorphometric analyses.



(a) Individual CN30 – young adult (18-29 years)



(b) Individual CN07 – older adult (50+ years)

7.5. REFERENCES CITED

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CHAPTER EIGHT: CONCLUSIONS

Trans-iliac bone cores were extracted from twenty-three females (age range 18-50+ years) to: (i) investigate the age-associated loss of trabecular bone quality in a medieval British skeletal sample, and (ii) to evaluate the methodological feasibility of utilizing trans-iliac bone cores in the histomorphometric examination of archaeological skeletal material. Each bone core was thin sectioned, mounted on microscopy slides and digitally photographed. The histomorphometric parameters of trabecular bone volume (BV/TV), thickness (Tb.Th), number (Tb.N) and separation (Tb.Sp) were then collected for each individual using the image analysis program Sigma Scan Pro 5.0. Additional measurements of bone quantity, expressed as bone mineral density (BMD), were also employed in this study. All bone quantity data were previously collected by McEwan and colleagues (2004) using a QDR 4500A dual energy x-ray absorptiometry (DXA) machine to quantitatively assess the one third, mid and ultra distal sites of the radius.

Ensuing qualitative and quantitative analyses reveal three distinct patterns of age-related reductions in both cortical and trabecular bone mass and structure. The first of these patterns is one of early onset trabecular bone loss – with statistically significant decreases in BV/TV ($p=0.016$) and Tb.Th ($p=0.013$) and increases in Tb.Sp ($p=0.02$) evident between the young and middle-aged women of this sample. It is postulated that these significant losses are attributable to secondary causes, specifically those associated with inadequate nutrition, reproductive stresses and low body weight. In contrast, the second and third patterns, notably the statistically significant decreases in radial bone quantity (McEwan et al., 2004) and non-statistically significant modifications in iliac bone quality, are observed between the middle-aged and older women of this sample. Given the age range of these individuals, it is hypothesized that these modifications represent menopausal changes to the skeleton. That these changes did not result in osteoporotic fracturing of the wrist and hip, common occurrences in contemporary female populations, indicate that the fracture risk of these medieval women was somehow alleviated. It is suggested that the arduous daily physical activity experienced by these women diminished their osteoporotic fracture risk. However, this diminishment did not occur through the minimization of bone loss – a common clinical supposition - but possibly through the augmentation of muscular strength and coordination thereby curtailing the falls which precipitate these fracture types.

The preceding results illustrate the methodological feasibility of utilizing trans-iliac bone cores for the histomorphometric examination of age-associated bone loss in archaeological skeletal material. Of the thirty-one females initially selected for examination twenty-three were sampled successfully, with the bone cores of these individuals exhibiting nominal architectural distortion thereby permitting subsequent histomorphometric analyses of the bone. Trans-iliac bone cores are, therefore, recommended as a procedural option for bioarchaeologists interested in the examination of bone loss in past populations.

A final finding of this research is the identification of a pathological individual, a middle-aged female identified as G275. The combined qualitative, quantitative and radiographic examinations of several investigators led to a differential diagnosis of renal osteodystrophy in this individual. It is hypothesized that this woman suffered from

chronic renal impairment leading to the development of secondary hyperparathyroidism and abnormal indices of cortical and trabecular bone mass and structure. The probable identification of renal osteodystrophy in this skeletal sample highlights the importance of utilizing multiple diagnostic techniques on both cortical and trabecular sites to identify aberrant individuals.

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